HOMEOSTASIS

- Term coined by W.B. Cannon
- Homeostasis – maintenance of internal environment

  → **Interstitial fluid of ECF**
- There are two systems that maintain homeostasis

Feedback system
↓
There is always a stimulus
↓
Stimulates sensors
↓
Effectors
↓
Effect

Feedforward system
↓
No sensor / stimulus
↓
Working in anticipation

- Feedback mechanism → 2 types

Negative
↓
(say) Exercise
↓
BP increase from 120mmHg → 160 mmHg
↓
Sensed by baroreceptors
↓
Activation of NTS / UMC / CIC
↓
Decrease BP → 140 mmHg

Positive

- $$\text{Gain} = \frac{\text{Correction}}{\text{Error}} = \frac{160 - 140}{140 - 120} = \frac{20}{20} = 1$$

Gain will check the efficiency of the effectors

Eg: 120 → 160 → Gain $\frac{C}{E}$ = 3
↓
130

- Error is 0, Ⓠ Gain = $\frac{C}{E} = \frac{C}{0} = \infty$
- Gain is infinite in kidney for correcting BP blood volume (RAAS Mechanism)
- Suppose normal blood glucose – 100 mg/dL
↓ intake of sugars
(Insulin release immediately)
150 mg/dL
↓
120 mg/dL

$$\text{Gain} = \frac{C}{E} = \frac{150-120}{120-100} = \frac{30}{20} = 1.5$$

- Suppose TSH is there, TSH stimulates T_3 and T_4 inhibits TSH

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- GnRH → stimulates FSH and LH

Stimulates Sertoli cells
↓
Inhibin released
↓
inhibits

Leydig cells
↓
Testosterone
↓
inhibit Leydig cells

Positive feedback 00:10:27

- Increase of stimulus isn't decreasing the response, but actually increasing the response
- C – Coagulation Cascade
- L – LH surge during Ovulation
- A – Action potential → Influx of Sodium increases until gates close
- P – Parturition → Increase uterine contraction → dilates cervix
  ↓
  Oxytocin released → Increase uterine contraction
- S – Shock → BP decrease → Shock decrease

Feedforward Mechanism 00:12:25

- Works in anticipation without a stimulus
- System will anticipate and takes corrective measures
- E.g., – Decreased body temperature is sensed by skin → Shivering is initiated
- BP & HR increase → Before Exercise
- Cerebellum activates cells in feedforward mechanism

Granular cells → Stellate cells → Purkinje cells

Basket cells

Golgi cells

CELLULAR FLUID

- Total body water – 60% of body weight

2/3 ICF (40%)　　1/3 ECF (20%)

15% ISF　　5% plasma

- Blood = 8%
  - 5% plasma
  - 3% blood cells
- Total blood volume = $\frac{\text{plasma}}{1 - \text{Hematocrit}}$

Eg: Plasma = 3L

Hematocrit – 50%

$$BV = \frac{3}{1-0.5} = \frac{3}{0.5} = 6L$$

- Transcellular fluid (<1%) → Fluid inside a territory
  - Synovial fluid
  - Pericardial fluid
  - Pleural fluid
  - Intraocular
- Males have 10% greater water than female (Because of increase fat in females)
- Lean by body mass → 70% TBW
- TBW decrease with age
- ~~ECF~~ = more in infants → more prone for dehydration

ICF

- By 3-4 months → ECF almost equal to ICF

  > 1 year → 2/3 ICF, 1/3 ECF

Body Fluid Measurement 00:08:08

- Volume of distribution principle / also called as indicator dilution method
- $$V = \frac{Q - e}{C}$$

  V = Volume

  Q = Quantity of indicator 30g

  E – elimination on indicator 3

  c– concentration of indicator 10

  eg: $\frac{30-3}{10\,mg/dL}$

  $\frac{27 \times 1000}{10}$

  = 2700dl

Indicator

1. TBW
   - Deutrium oxide
   - Titrium oxide
   - Antipyrine
2. EcF
   - Inulin
   - Sucrose

- Mannitol
- Sodium thiosulphate

3.ICF

- TBW – ECF
- Calculated indirectly

4.Plasma volume

- Evan's blue
- Radiolabelled albumin

5.ISF

- ECF – PV
- Calculated indirectly

- Approximately daily intake of water → 2100 ml ingestion and 200 ml
- Approximately daily loss of water → 700 ml (Insensible loss)

350 from skin   350 from lungs

- 100ml loss form sweat

- 100 ml – feces

- 1400 ml – urine formation

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Darrow's Yannet Diagram 00:16:04

1..

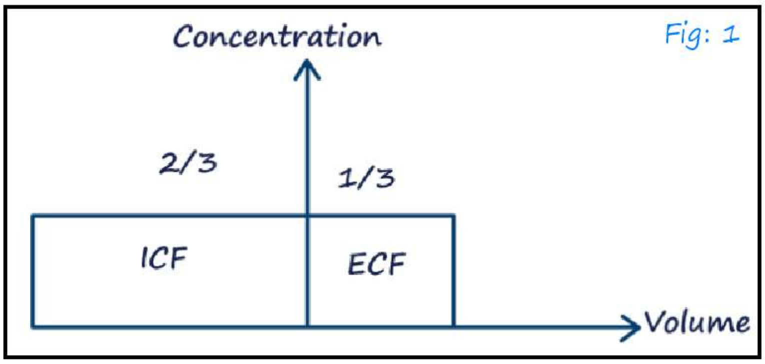
Fig: 1
Concentration
2/3
1/3
ICF
ECF
Volume

2.If there is gain of isotonic fluid

↓↓

Increase ECF

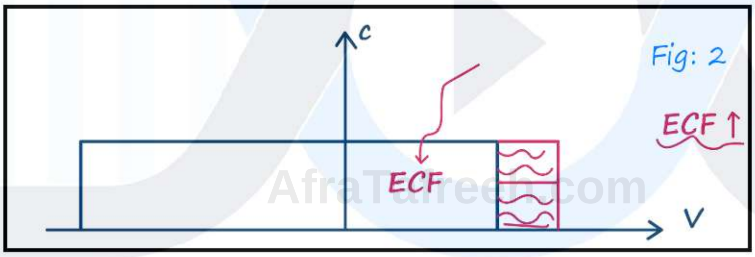
Fig: 2

3.Loss of isotonic fluid → Hemorrhage diarrhea

↓↓

Decrease ECG

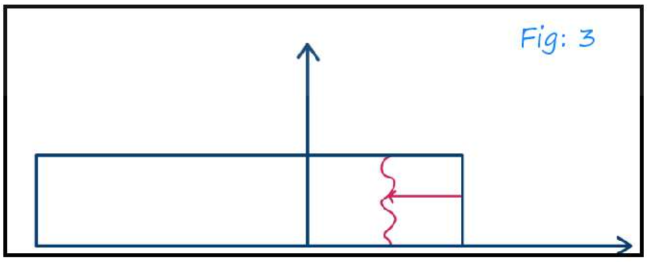
Fig: 3

4.Gain of hypotonic water → increase water SIADH

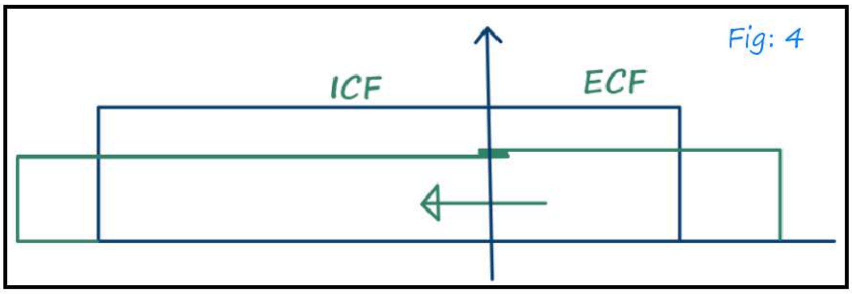

Fig: 4

- Concentration decrease → moves from lower conc. to high concentration
- osmolarity of ICF and ECF, both will decrease → ECF → ICF

5.Loss of hypotonic fluid → DI sweating

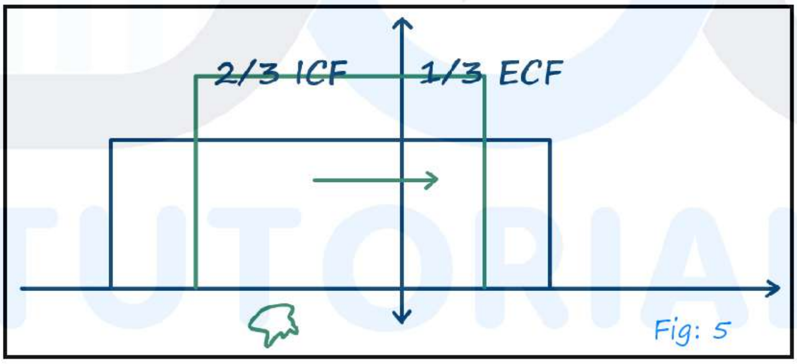

Fig: 5

- If fluid is lost → ECF becomes hypertonic

  ↓↓

  Water flows from lesser concentration to higher concentration
- Osmolarity increase
- Water moves from ICF → ECF
- Cell starts shrinking, water is lost → cellular degradation

6.Gain of hypertonic fluid → increase Nacl

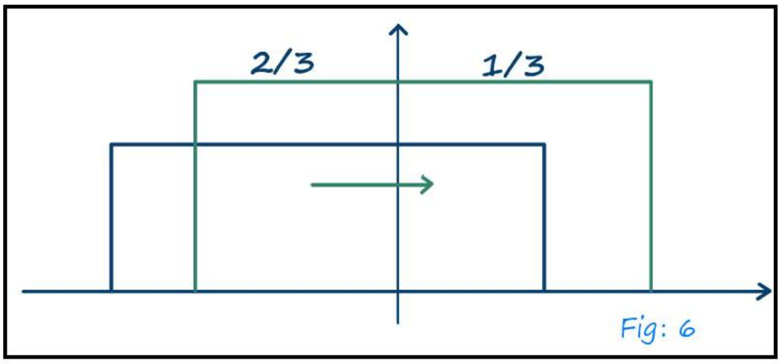

Fig: 6

- Volume is increasing and concentration is also increasing
- Water moves from lower concentration to higher concentration
- Osmolarity will increase

  ↓

  Water moves from ICF → ECF

  ↓

  Shrinkages of cell

7.Loss of hypertonic fluid

- If aldosterone is not working properly / In adrenocortical insufficiency

↓↓

Sodium will not be absorbed

↓↓

Loss of hypertonic fluid

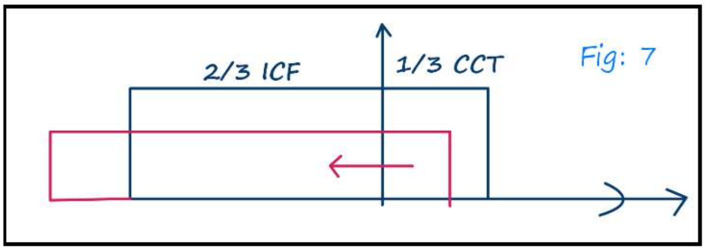

Fig: 7

- Volume also decreases and concentration decrease
- Water moves from lower concentration to higher concentration
- Osmolarity will decrease
- Water moves from ECF → ICF
- Lysis of cell ⊕

1.If there is water loss

- 2/3 ICF
- 1/3 ECF

2.If there is isotonic fluid

- ECF decrease
- No water loss from ICF

1.Plasma → ISF except plasma has more protein

2.Due to donnan effect, --. Protein attract more cations

P > ISF

ECF	ICF
• Na • Cl • Ca ⊗ pH: - 7.4 cl^-	• K^+ • Mg^{2+} ⊗ pH: - 7 $po4^-$, Proteins.

Osmosis

- Move of water wherever Na^+ is going
- Osmoles → determine osmolarity
- 1 mole → gram molecular weight

  Eg: 1 mole of Nacl – 23 + 35.5 = 58.5

  1 equivalent – gram molecular weight / valency

  Ca^{2+} = 40/2 = 20
- If cell is in hypertonic solution, water will go out → cell shrinks

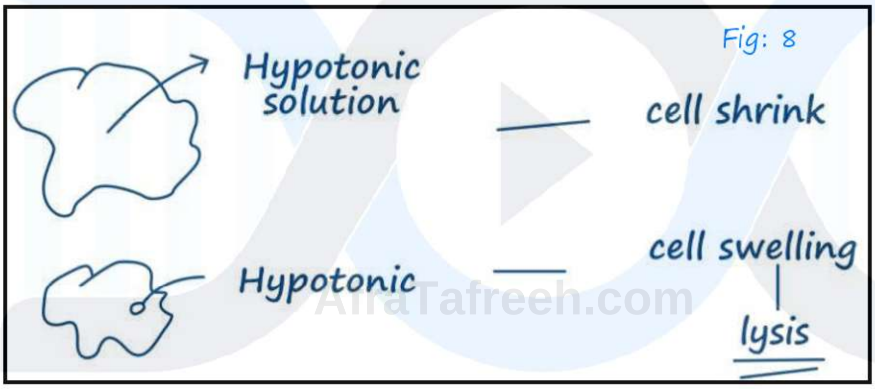
Hypotonic
solution
cell shrink
Hypotonic
cell swelling
lysis

Fig: 8

- If cell is in hypotonic solution, water comes inside → cell swelling
- Isotonic → 5% mannitol

  5% dextrose in water

  0.9% Nacl

  Ringer lactate / Hartmann solution

  ↓

  (~ plasma except magnesium absent)

  Ringer solution (RL – Na lactate)

- Normal osmolarity = 285 – 295 mosm/L

$$\frac{\text{Formula}}{0} = 2 \times \text{Na} + \frac{\text{Glucose (mg/dl)}}{18} + \frac{\text{BVN}}{2.8}$$

- Osmolar gap = Measured osm – calculated osm around 10

- $\text{BUN} = \frac{\text{urea}}{2.18}$

- Why proteins contribute less to osmolarity

↓↓

Due to lower molecular concentration and increase molecular weight

RECEPTOR PHYSIOLOGY

- Paracrine – one cell stimulating other cell 01→ 02
- Autocrine – one cell stimulates its own self o2
- Endocrine- cell going to blood circulation and stimulating distant organ or cell or tissue
- Term endocrine given by Starling
- 1st hormone to be discovered was secretin by Bayliss and starling

5 Types of Hormones 00:02:33

- AA derivatives
- Small neuropeptide
- Large neuropeptide/pH
- Steroid
- Vitamin A.D

Amino Acid derivatives

- Tyrosine - Thyroid
  - Epinephrine
  - Norepinephrine
  - Dopamine
- Tryptophan – serotonin
  - Melanosis
- Histidine – Histamine

Small Neuropeptide

- TRH- Glutamate + Histidine + proline
- GnRH- 10 AA
- Vasopressin Oxytocin – 9AA

Large neuropeptides /protein homes (> 50AA)

- Pituitary gland
- Pancreases + Erythropoietin → Synthesized in RER and modified in Golgi apparatus
- Parathyroid
  - No of A in insulin – 2
  - No of AA in PTH – 84

Steroid Hormone

- Basically cholesterol
- Synthesized in – adrenal cortex
  - Ovary
  - Testis
  - Placenta
  - Smooth EK
- C21 → progestins /corticoids
- C19 → testosterone
- C18 →
- All hormones have entered the nucleus either directly or through cell messenger DNA converted to RNA<, RNA converted to protein
- If they are protein and cannot get in to cell membrane, their receptor will be in the cell

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membrane, and called as cell meme brae receptors

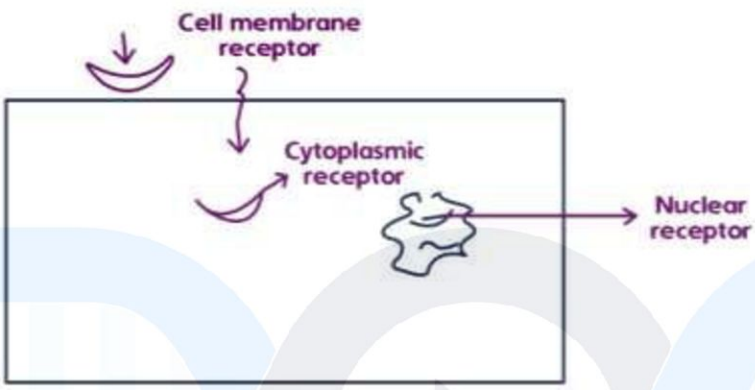
like – AA ligand

- Protein ligan

- If they can enter inside, they have receptor ins cytoplasm/nucleus

↓ ↓

Cytoplasmic Nuclear
Receptor


Cell membrane receptor
Cytoplasmic receptor
Nuclear receptor

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Cell membrane receptor

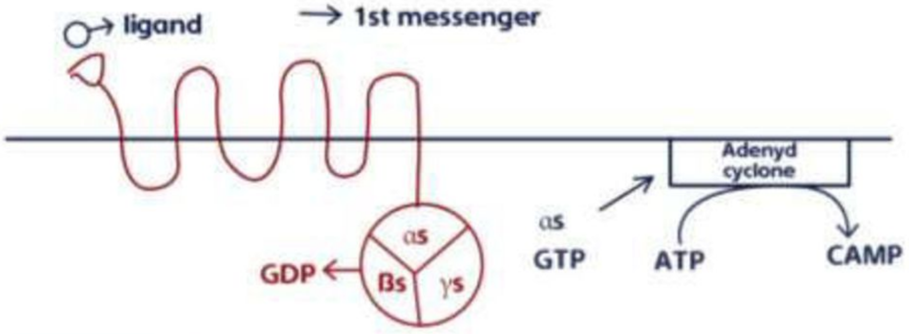
- GPCR
- Receptor tyrosine kinase
- TAKE or JAK SATA or Cytokines
- R serine/ threonine kinase

- GPCR
  - → G protein coupled receptors
  - → largest family of receptors
  - → Also called serpentine receptor or seven pars' receptors

↓

Nobel prize was given of this discovery in 1994 to Alfre d Gillman

- Broadly divided → G stimulatory (GS)
  → G inhibitory (Gi)
  → G1


ligand
1st messenger
Adenyd cyclone
αs
GTP
ATP
CAMP
GDP
αs
Bs
γs

- Ligands are any chemical which attach to the receptor to do some biological action
- When ligand attaches

↓

GDP converted to GTP

↓

α s takes up GTP and reaches Adenyl cyclase

↓

Adenyl cyclase with help of α s GTP coverts ATP → CAMP (2nd messenger)

↓

Cause phosphating of protein → does multiple physiological action depending on ligand 2 location n

↓

Kinase A

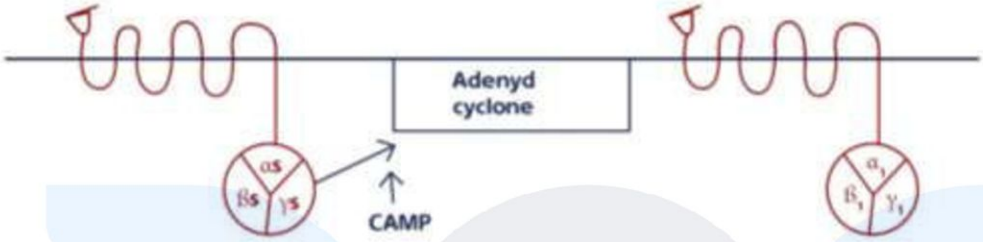
↓

Tertiary messenger

- CAMP → AMP

  ↓

  Phosphodiesterase
- α s has intrinsic GTPase activity → converts all GTP → GDP


Adenyd cyclone
αs
βs
γs
CAMP
α_i
β_i
γ_i

- Adenyl cyclase in sandwiched between GS and H
- α → Adenyl cyclase

  ↓

  Increase CAMP

  ↓

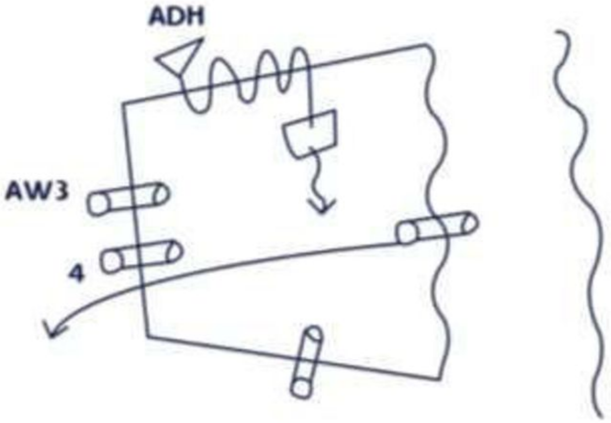
  phosphating of protein kinase A
- α i → Adenglyclase

  ↓

  Decrease CMP

  ↓

  Dephosphorylation of protein kina\se A



- e.g.: when ADH combines with GS → enter then cell

  ↓

  Implants aquaporins on sides of Lumen

  ↓

  Water is absorbed

- In heart, B1-GS → increase CAMP → increase HR

  M2 - G1 → decrease CMAP → decrease HR

Cholera toxin → 2 units

A

Monomeric enzymatic moiety → Active

↓

ADP Ribosylation of GSα

↓

Continuous activation of adenyl cyclase

↓

Increase CAMP

↓

Phosphorylation of protein (FTR gene) → cystic fibrosis transmembrane receptor

↓

Chloride channel

↓

Increase choired secretion in human of intestine

↓

Na/H2o → diarrhea

B

Binding unit → pentameric

↓

Binds with Gm, ganglioside in intestinal epithelia cell

↓

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- ONN → permanently ONN
- Perturis toxin → inhibit Gα 1→ increase CAMP

↓

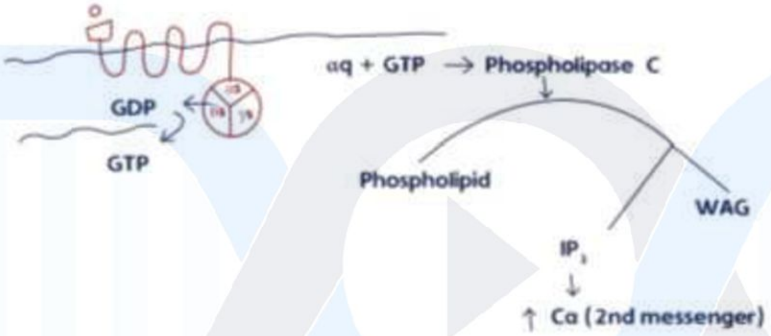
Increase secretion

↓

Whopping cough

- ON switch parament ON – cholera toxins
- Off switch OFF means – peritries

Increase adenyl cyclase


GDP
GTP
αq + GTP → Phospholipase C
Phospholipid
WAG
IP₃
↑ Ca (2nd messenger)

Example

- Gs → – ADH (V2 –CD)
  - Epinephrine /(P1)
  - Norepinephrine
  - Glucagon
  - TSH/FSH/ACTH/PTH/MSAH/corticotropic releasing hormone /secretin/calcitonin
  - β1/β2/β3→ Adrenergic

- Gi → – somatostatin
  - Angiotensin II
  - α 2
  - Muscarine (M2, M4)

- Gq→ – All releasing hormone except CRH
    - TRH/GnRH/oxytocin/CCK
    - M1, M2, M5

Diseases due to mutation in GPCR

Mc cure Albright syndrome

- Gain of mutation of GS α
- 3P's – precocious puberty) due to gonadotrophins)
    - Polyostotic fibrous dysplasia (PTH)
    - Pigmentation (MSH)
    - Pseudohypoparathyroid

CELL MEMBRANE

Cell membrane 00:00:18

- Fluid- Mosaic Model- given by singer & Nicolson
- "Lipids are like- sea, proteins are floating like- Iceberg"

Lipid	Protein	Carbohydrate
40%	55%	5%

- Usually, proteins > lipids in cell membranes but in myelinated neurons have more lipids than proteins

Lipid 00:02:40

Lipid

Phospholipid Glycolipid cholesterol

- Maximum

Lecithin/phosphatidyl choline

- It is the component of surfactant
- Its deficiency causes respiratory distress syndrome /hyaline membrane disease
- It is more in surfactant

Sphingomyelin:

- It is less in surfactant
- If lecithin to sphingomyelin ratio is more than 2 then we say lung is matured
- Test → shake bubble test → we take amniotic fluid and shake it. It bubbles are formed then it is more of lecithin

Phosphatidyl serine:

- It is present on the inner side of cell membrane, if it is seen on outer surface of the cell membrane
- It indicates apoptosis→ annexin – V stage

Inositol Triphosphate (IP_3)

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- Gq receptor present in the cell membrane → activates αq → activates phospholipase – C

↓

(converts) phospholipid

(IP3) DAG

↓

Secondary

messenger to Gq

Cardiolipin

- Mostly present in mitochondria of heart muscle
- In VDRL we test for anticardiolipin antibodies to diagnose syphilis

Glycolipids 00:09:12

In CNS
↓
Cerebrosides

In GIT
↓
gangliosides

- Cholera toxin –
  - B- Subunit – Pentameric → Binds GM-1 ganglioside of intestine
  - A- Subunit – Monomeric
    ↓
    Increases Cl
    ↓
    Causes cl+ Na + H2o release in lumen causing diarrhea

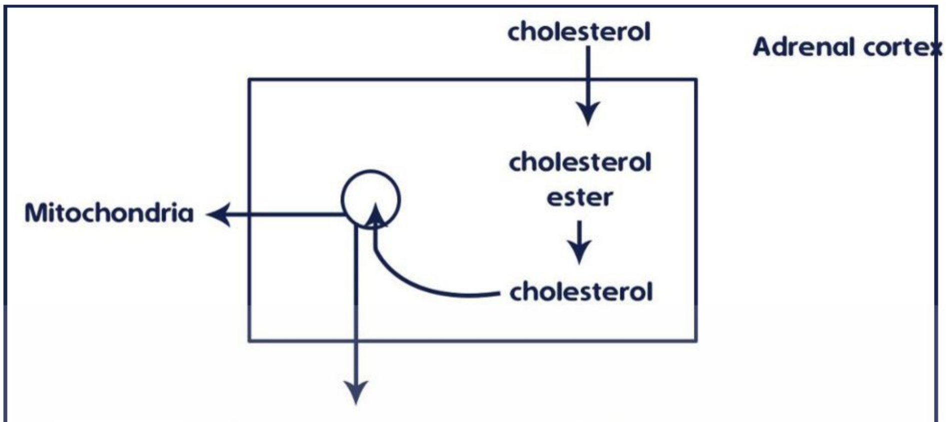
Cholesterol 00:11:40

- It is called as fluidity buffer- maintain fluidity
- Raw material for Vitamin – D3
- 7- dehydrocholesterol

↓ UV rays

Cholecalciferol
↓
25(OH) cholecalciferol (liver)

- Vitamin D3 → 1, 25 (OH2) cholecalciferol (kidney)
- Raw material for steroid hormones


cholesterol
Adrenal cortex
cholesterol ester
cholesterol
Mitochondria

Activates transcription factors which helps in formation of steroid hormones

Fig: 1

Fatty acids increase fluidity Vs decrease fluidity

Increase fluidity

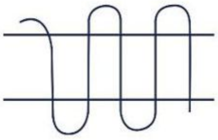
→ PUFA
- Linoleic acid
- Linolenic acid
- Arachidonic acid

Decrease fluidity

→ saturated fatty acids
- Steric acid
- palmitoic acid

Proteins 0016:10

Span cell membrane

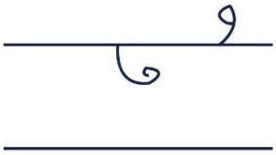


Integral proteins

Cantel

E.g. – GPCR
- Na, K ATpase pump
- CFTR

Attached – Outer
Inner



Peripheral proteins
- Cell surface receptor either outer or inner
- Calles as supporting proteins

RBC

skeletal Muscle

Dystrophin
- Spectrin → if mutated
  - Hereditary ellliptocytosis
- Ankyrin → it mutated
  - Hereditary sphero cytosis

Lipid anchored proteins
- Exclusively preset on RBC
- GPI (glycosyl phosphatidyl inositol)
- CD55 CD 59

↓ –

PNH
- Paroxysmal nocturnal hemoglobinuria
- Treatment: – block MAC Eculizumab

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Dystrophin

Mutation

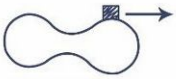
DMD
↓
Duchenne Muscular dystrophy

BMD
↓
Becker's muscular dystrophy

- Gower sign → if we ask the child to standup from sitting position – child will rise on his own limb
- Calf pseudohypertrophy

Carbohydrates 00:25:00

N– acetyl galactosamine + → Blood group 'A'



Galactosamine + → Blood group 'B'

Both + → blood group 'AB'

If both are absent – Blood group 'O'

Cell skeleton 00:26:28

Microtubules
Microfilament
Dynamic cytoskeleton

Intermediate filament
↓
Static cytoskeleton

Microtubules → Bigger

Kinesin	Dynein	Tubulin
Anterograde movement	Retrograde movement	Help in movement of chromosome ↓ So, these blockers are used in cancer – vincristine – Vinblastine

Microfilaments

Actin Myosin

- They are important for skeletal muscle contraction
  ↓
  Sliding filament theory
- Cell motility – G - actin – monomer
  F - actin – polymer
- Mechanism of moment → action polymerization
  e.g.: listeria monocytogenes – polymerized tail present and movement is called as tumbling motility

Molecular motors

- Kinesin
- Dynein
- Myosin
- Dynamin
- Actin is not a molecular motor

Static cytoskeleton

- Intermediate filament
- Desmin → found in muscle cell → tumor marker for sarcoma (myosarcoma)
- Keratin → found in epithelial cell → tumor marker for carcinoma (cytokeratin)
- Intermediate filament deposition in liver → Mallory Dank bodies
- Laminin → seen in nucleus of cell

  ↓ mutation

  Pre mature ageing (progeria)
- Vimentin → Fibroblast /connective tissue

  → Tumor marker of mesenchymal origin
- GFAP – Glial Fibrillary Acidic Protein
  - Tumor marker in Gliosis /Astrocytoma

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Intercellular junction 00:37:30

- Connecting cell to cell

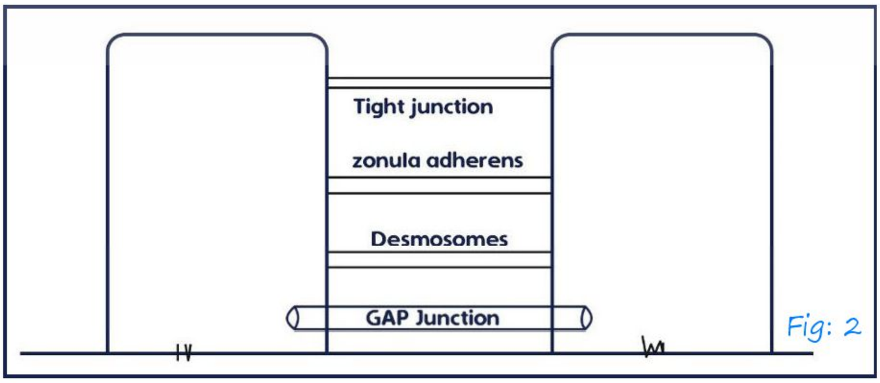

Fig: 2

Tight junction /zona occludes

- Made up of claudin/occludin
- Found in kidney, intestine, Blood Brian barrier, choroid plexuses
- Kidney
  - PCT- Leaky- paracellular transport occur easily
  - DCT- Tight

Zona adherens

- Attach with actin

Desmosomes

- Attach to intermediate filament
- Seen in area of stress
  - Uterine cx
  - Skin
  - Heart

Proteins
- Desmoglein
- Desomocollin

Gap junctions

- Made up of protein → connexon
  ↓
  Made up 6 subunits (connexin)
- They are present in heart, smooth muscle, neurons
- Mutation to connexon to "Charcoat Merry tooth disease"
- Cardiac gap junctions are present in intercalated disc
- Connecting cell to basement membrane
  - Hemidesmosome
  - CAM (Cell adhesion molecule)

Hemidesmosome	CAM
Connects cell to basement membrane	• Cell adhesin molecule • Selectin • Integrin • Cadherin

Membrane fluidity is increased by

a. Palmitic acid
b. Linoleic acid
c. Myristic acid
d. Stearic acid

Gap junctions are found in all except:

a. Skeletal muscle
b. Smooth muscle
c. Cardiac muscle
d. Neurons

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An absent dynein arm in cilia can lead to all of the following except:

a. Asthma
b. Chronic sinusitis
c. Situs inversus
d. Bronchiectasis

The force generating proteins are

a. Calmodulin and actin
b. Myosin and myoglobin
c. Dynein and kinesin
d. Troponin and dynamins

Identify the incorrectly matched pair of intercellular connections and their structural units

a. Hemidesmosome – Integrins
b. Desmosome – Desmoglein
c. Gap junctions – Cadherins
d. Zona occludens – Claudins

Which of the following is an example of peripheral protein?

a. Sodium potassium ATPase pump
b. Tyrosine receptor
c. Cell surface receptors
d. G-Protein coupled receptors

TRANSPORT ACROSS CELL MEMBRANE

- Active
  - Primary
    1. Na^+ K^+ ATPase
    2. HK(proton) pump
    3. SERCA
  - Secondary
    - Symporter (Or) co-transporter active transport against concentration gradient ATP is used.
    - Antiporter (Or) Counter transporter passive transport ATP is not used. It is along concentration gradient
- Passive
  - Diffusion
  - Facilitated

Na^+ K^+ ATPase 00:03:50

- Most common pump present in all living cells
- It is a heterodimer
  - α subunit (α_1, α_2, α_3)
  - β subunit (β_1, β_2, β_3)
- β subunit contains 3 ecf glycosylation site for attachment to carbohydrate residue.
- α subunit have
  - ECF site: gives attachment to two K^+ and ouabain
  - ICF site: gives attachment to three Na^+

  Electrogenic coupling ratio : 3:2

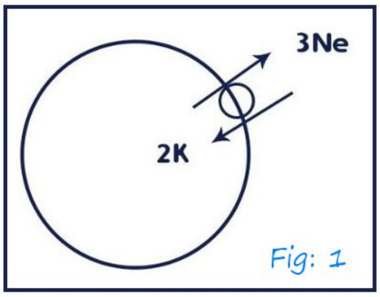


Fig: 1

Note:

- The main function of this pump is to regulate cell volumes
- RMP maintenance is secondary function

Hormones stimulating Na^+ K^+ pump:

- Insulin (therefore cause influx of K^+ leading to hypokalemia)
- Thyroid hormone
- Aldosterone

Inhibitors of Na^+ K^+ pump:

- Digitalis
- Ouabain

Proton pump 00:11:40

- Metabolic acidosis leads to hyperkalemia. Therefore, K^+ is exchanged for H^+

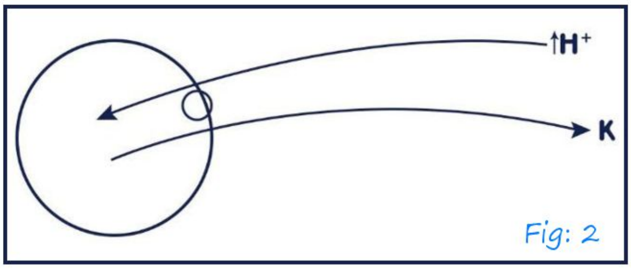


Fig: 2

- Hyperkalemia causes metabolic acidosis. Therefore, increase K^+ causes H^+ efflux and K^+ influx

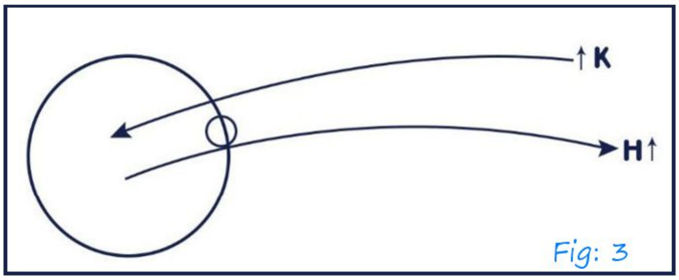


Fig: 3

- Similarly metabolic alkalosis causes hypokalemia.
- Serca
  - It causes active transport of ca^{+2}

Secondary active transport 00:15:08

- Energy is utilized

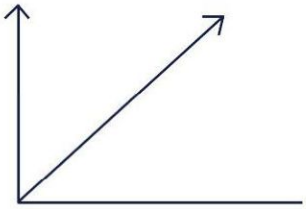
Symport	Antiport
Both molecules travel in same directions	Molecules travel in opposite direction
Eg: SGLT 1 and 2	Eg: NA H exchanger

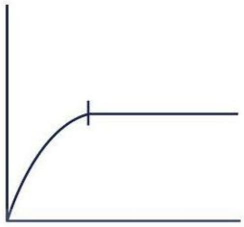
Uniporter : only single molecule transported along the direction

Passive transport 00:20:20

- ATP / Energy not utilized in this mode of transport

Simple Diffusion	Facilitated Diffusion
ATP not needed	ATP not needed
No carrier proteins	Carrier proteins present
Follow ficks law of diffusion	Follow michales menton diffusion
No T max	T max present





Note

ficks law of diffusion

$$v = \frac{\Delta P \times A \times D}{T}$$

V- rate of diffusion

V $\propto$ pressure difference

$\propto$ surface area

$\propto$ 1/thickness

$\propto$ diffusion coefficient (DC) / partition coefficient

$$\text{diffusion coefficient} \propto \frac{\text{solubility}}{\sqrt{\text{molecular weight}}}$$

Eg: GLUT (Glucose Transporter)

GLUT1: Blood Brain Barrier RBC, placenta.

GLUT2: β Cell, Liver, Intestine, Kidney

GLUT4: Muscle, Adipocytes

↓

Insulin Dependent

1. All channel protein and many carrier proteins allow cell membrane to cross passively
2. Carrier proteins using ATP are called pumps.

Ionophore 00:27:50

- These are synthesized by micro-organism to import ions into cell

  Example: Ionomycin – for Ca^+

  Valinomycin – for K^+

Osmosis 00:29:23

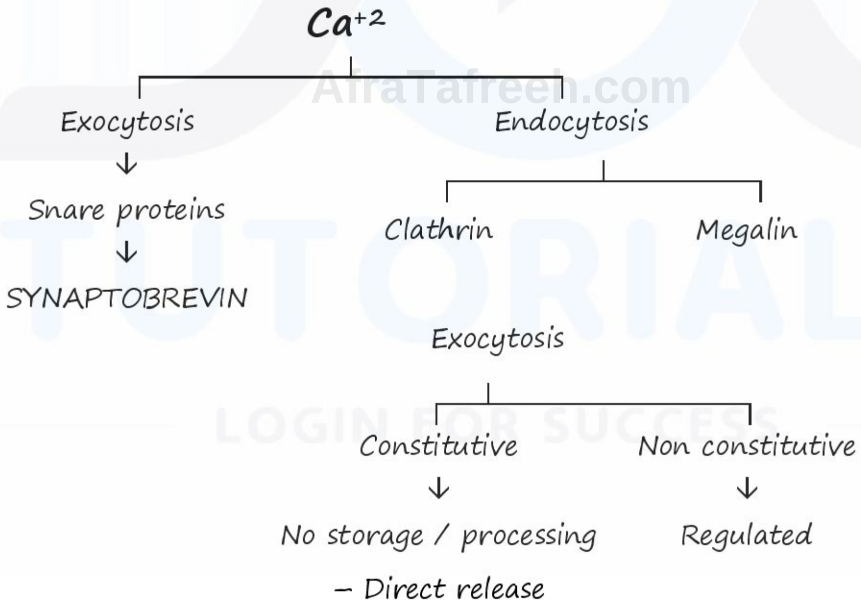
- It is passive process
- Water flow along the gradient (Solvent drag – caused by Na^+)

Note

- Plasma osmolarity = 280-300 mosm/L
- Plasma osmolality = 280-300 mosm/kg

Vesicular transport

- It is an active process, ATP are utilized to move vesicle


Ca^{+2}
Exocytosis
Endocytosis
Snare proteins
SYNAPTOBREVIN
Clathrin
Megalin
Exocytosis
Constitutive
Non constitutive
No storage / processing
– Direct release
Regulated

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CELL ORGANELLE

Endoplasmic reticulum 00:00:20

- 2 types

1.Rough ER / Granular ER

↓

Have ribosomes

a. Synthesis of proteins

b. Folding of proteins

↓

Chaperons

↓

Heat shock protein

Misfolding proteins

↓

- Aβ amyloid – Alzheimer disease
- CJ DS (Creutzfeldt Jacob disease)

c. Degradation of proteins

Protease needed for degradation of proteins

2.Smooth endoplasmic reticulum

↓

Steroid hormone formation

TUTORIALS LOGIN FOR SUCCESS

SER

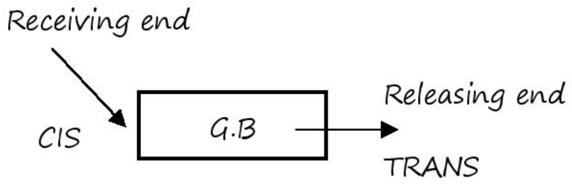
- Cytochrome 450 → Present in liver

→ expressed in SER

SER → Calcium storage

Golgi body 00:05:31

- Usually work with RER



- CIS part of golgi apparatus in towards endoplasmic reticulum
- Golgi apparatus receive proteins for 2 functions

Post translational modification
↓
Glycosylation of protein done
↓
Stability

Sorting of the protein
↓
Tagging is done via mannose-6-phosphate
↓
Lysosome

- Endoplasmic reticulum and golgi body are working together, hence called twin body / twin organelle

Lysosomes 00:09:10

- Main function is to destroy substances by creating acidic environment
- Needs protons and proton channels, enzymes like acid hydrolases acid lipases

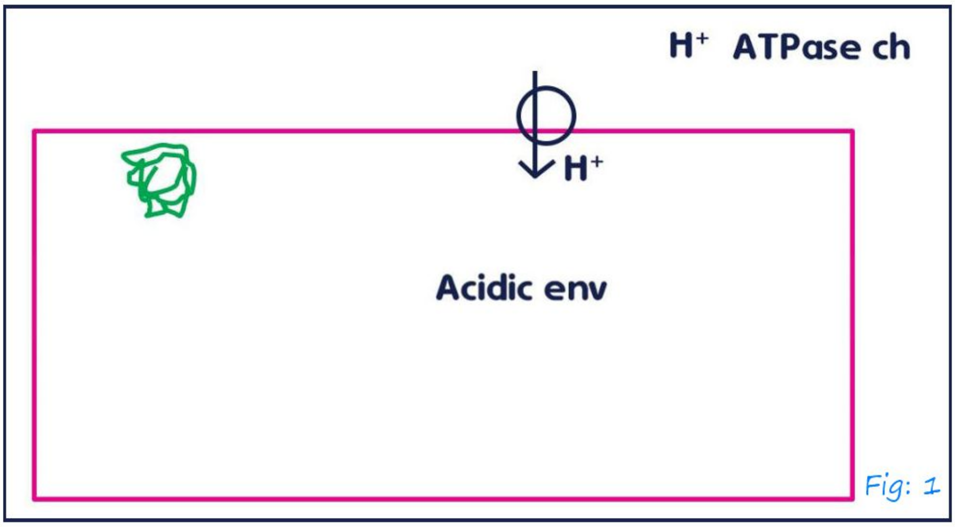


Fig: 1

- Also called as suicidal bag/ residual body (as residues are left)
- Very important for survival during starvation by eating our own

organ (Autophagy)

↓

Destroy mitochondria

↓

Use protein for energy

Peroxisome 00:12:29

- Peroxisome has catalase enzyme for destruction of free radical
- Also important for lipid metabolism
- Cause catabolism of very long chain fatty acids and branched chain fatty acids

- Defect in function of peroxisome – damage to myelin

CNS   Adrenal Cortex

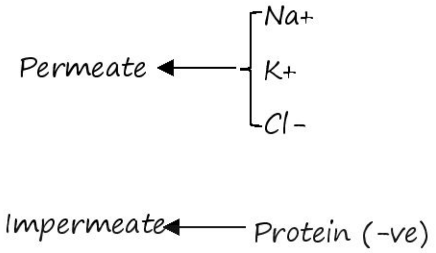
↓

Adrenoleukodystrophy

- Peroxisome disorder
  - Refsum disease
  - Zellweger syndrome/ disease

POTENTIALS

Donnan effect 00:00:38


Permeate
Na+
K+
Cl−
Impermeate
Protein (−ve)

- Principle : Presence of impermeate ion will affect the distribution of permeate ion

Nerst law of diffusion 00:04:02

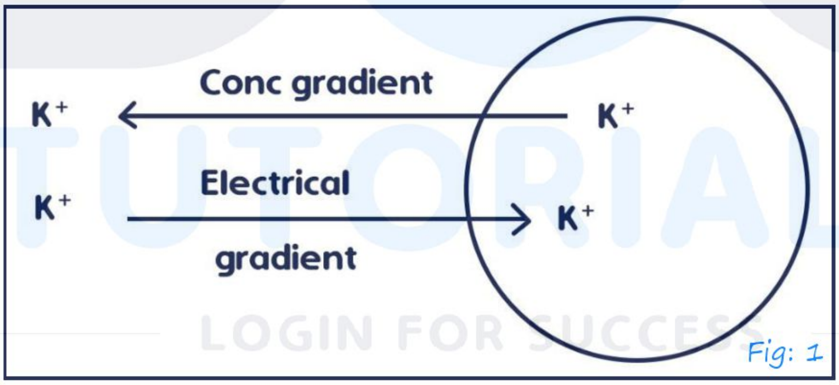

K+
Conc gradient
K+
K+
Electrical gradient
K+

Fig: 1

- conc gradient = electrical gradient then no net flow of ions
- Potential at which this grade is achieved

– Nernst potential (E) = $\frac{-23\ RT}{ZF} \log 10 \frac{Cl}{Co}$

$$\downarrow$$

$$E = \pm 61 \log 10 \frac{Cl}{Co}$$

- E values oR
  - Na^+ = +65
  - K^+ = – 90
  - Cl^- = – 70
  - Ca^{2+} = + 135

RMP 00:08:15

- Present in every living cell
- Negative charge present inside the cell membrane

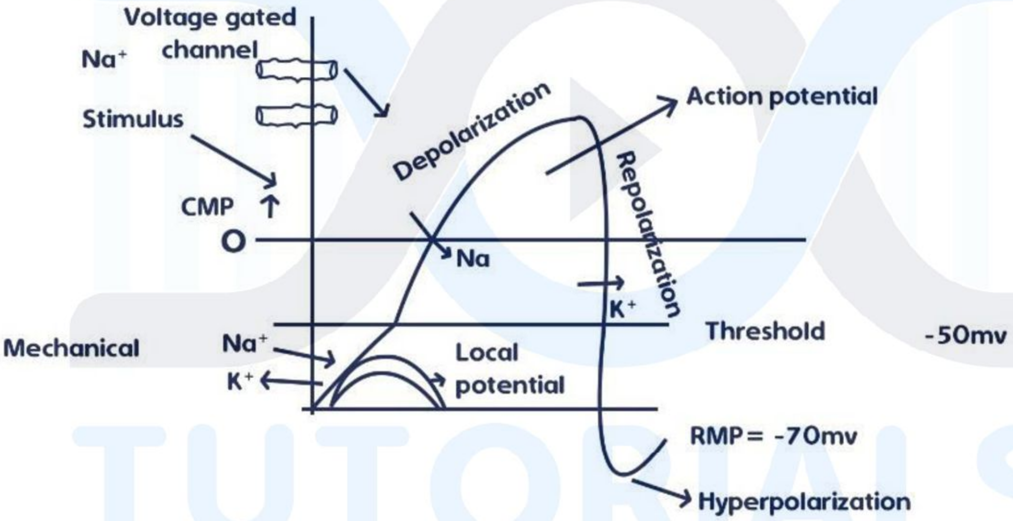
– ve – ve – ve – ve –ve –ve → RMP

- Generated by difference in permeability of cell membrane to different ions
  - K+ >>>>> Na^+
  - E_{k+} = – 90 mV
  - RMP ≈ EK = – 90 mV
  - RMP of neurons = – 70 mV

	RMP	Threshold
SAN	–50 mV	–40 mV
AVN	–60 mV	–40 mV
Myocardium	–90mV	–65 mV
Purkinje	–80 mV	
Smooth muscle	–55 to – 40	–40 mV

	RMP	Threshold
Skeletal muscle	-90mV	-55 mV
Neurons	-70 mV	-55mV
RODS	-40mV	
RBC	-12 mV	

Action potential 00:14:40


Voltage gated channel
Na+
Stimulus
CMP
O
Mechanical
Na+
K+
Depolarization
Na
Local potential
Action potential
Repolarization
K+
Threshold
-50mv
RMP= -70mv
Hyperpolarization

- Mechanical gated channels
- Voltage gated channels
- Ligand gated channel

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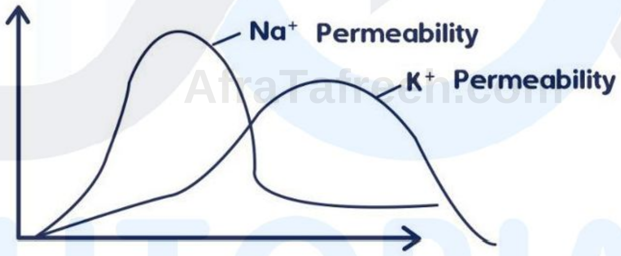
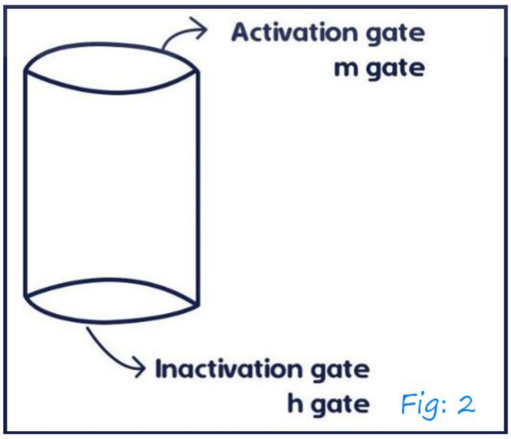
Local potential	Action potential
• Below threshold	• Above threshold
• Mech. Gated channels	• Voltage gated channels
• Doesn't follow all or none law	• Follows all or none law
• Summation +	• Summation not possible • Propagated
• Not propagated	
• LP/Electronic /graded potential	
	

Gate theory 00:25:49



Activation gate
m gate
Inactivation gate
h gate

Fig: 2

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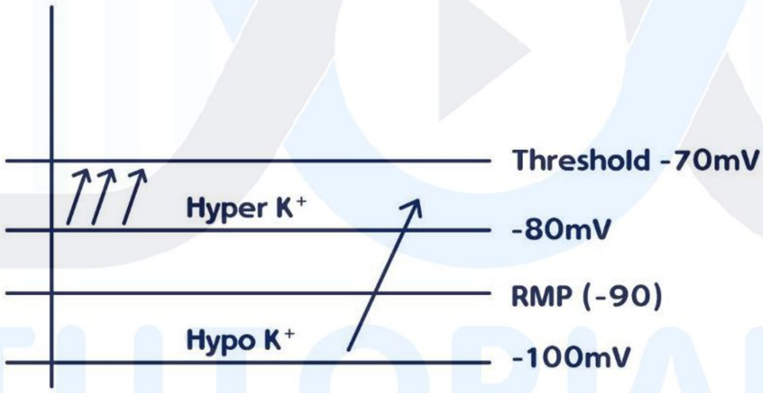
	Resting	Depolarization	Absolute refractory period
M gate	Close →	Open →	Open
H gate	Open →	Open →	Close

Hyperkalemia→ RMP decrease

Hypokalemia → RMP increase


Threshold -70mV
Hyper K⁺
-80mV
RMP (-90)
Hypo K⁺
-100mV

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Adaptation

- Repeated suprathreshold stimuli is not able to produce response

Accommodation

- Repeats subthreshold stimuli is not able to produce response

E.g. Hyperkalemia

- Treatment: - Calcium gluconate → stabilizer for Voltage gated Na^+ channel
  - Insulin
- Calcium guards the voltage gated Na+ channel
  ↓
  Stabilizes membrane excitability
- Hypercalcemic – stabilized membrane excitability
- Hypocalcemia – increase excitability – tetany - Carpopedal spams
- Decrease Na+ - decease size/amplitude of Ap
- Increase Na+ - increase size/amplitude of Ap

No effect on RMP

SKELETAL MUSCLE PHYSIOLOGY

Skeletal muscle

Contractile Protein   Regulatory Protein   Structural Protein

Contractile protein

- Actin

G → Monomer Actin

F → Polymer Actin

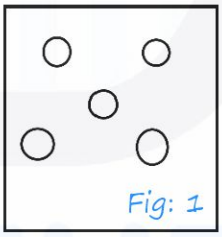


Fig: 1

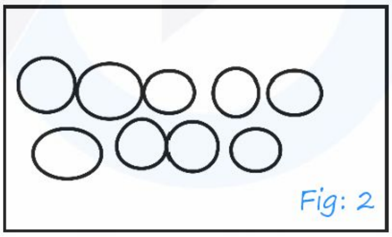


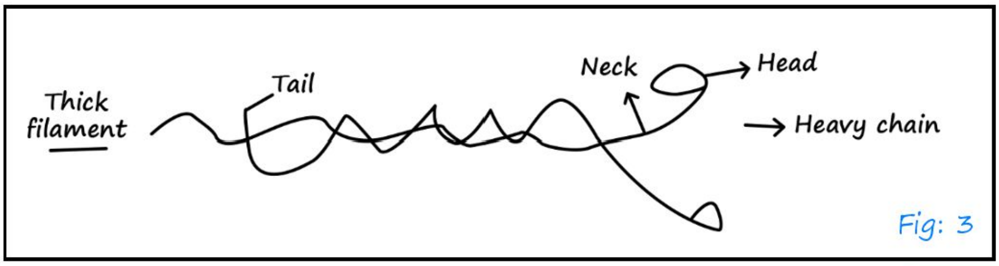
Fig: 2

- Myosin
  - Hexamer protein
  - Forms heavy chain

    2 MHC (Myosin heavy)

    2 MLC (Myosin light)

    2 MRC (Myosin chain)


Thick filament
Tail
Neck
Head
Heavy chain
Fig: 3

In heavy chain, you can notice head, neck, tail

- Length of myosin chain → 1-6 μm
- Head has
  - ATP binding site
  - Actin binding site
- Thin filament composed
  - Actin
  - Tropomyosin
  - Troponin

Regulatory protein

- Tropomyosin
  - Extends over entire actin filament in helical manner
  - Cover myosin binding site on actin
  - Helps in relaxation

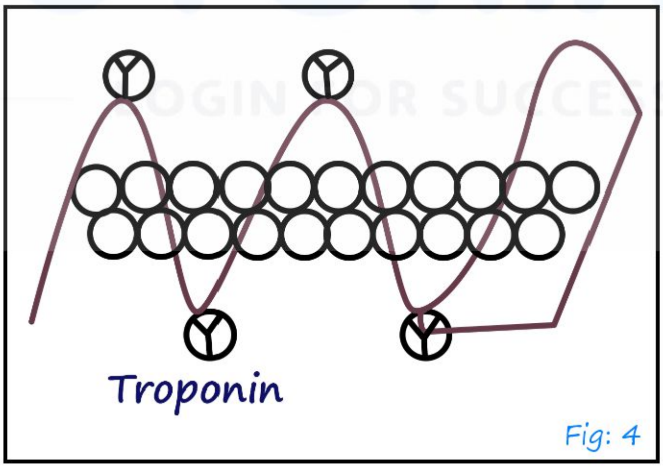


Fig: 4

- Troponin

  - Troponin has 3 subunits

  ↓

  T → Binds with tropomyosin

  I → Inhibit actin – myosin binding

  C → only when ca^{2+} comes, attach with troponin-C

  ↓

  Confirmational change

  ↓

  To uncover myosin binding site on actin

  ↓↓

  Actin and myosin cause contraction

Structural protein

- Our myosin surrounded by 6 actin

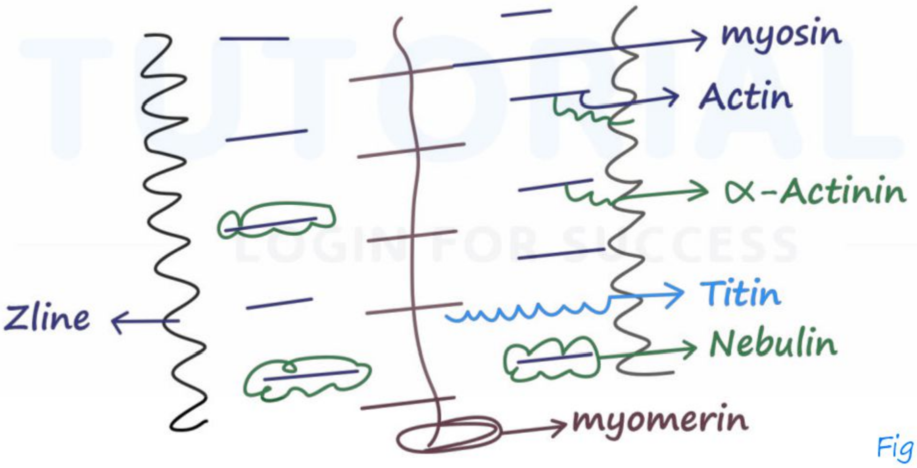


Fig: 5

- Protein which connects actin to 2 line – α actinin
- Protein which connects myosin to 2 line – Titin
- Protein which coraps around actin – Nebulin
- Centre protein is called myomesin
- Protein which gives stability – Dystrophin

Dystrophin – sarcoglycan complex

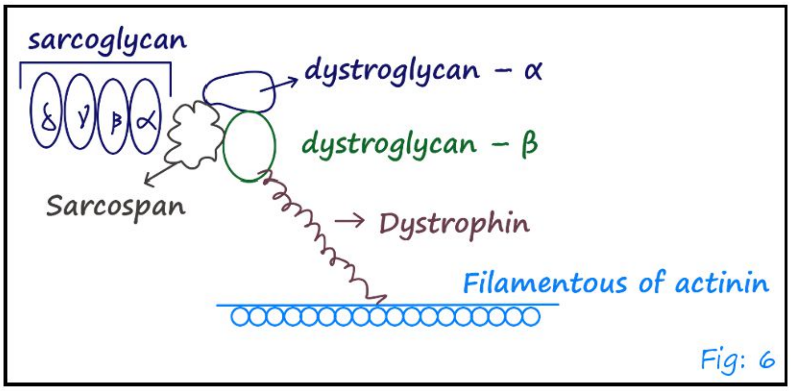

sarcoglycan
δ
γ
β
α
dystroglycan – α
dystroglycan – β
Sarcospan
→ Dystrophin
Filamentous of actinin

Fig: 6

- Contraction of muscle is converted into movement by dystronin
- Actin is binded to dystroglycan – β by Dystrophin
- If there is mutation of Dystrophin

DMD → Ducchene muscular dystrophy   BMS → Becker MS (Mild)

Gower sign

↓

- Patient climbs on own limb cohen trying to stand from sitting position → pseudohyperty of carf muscle
- Patient dies of respiratory palsy

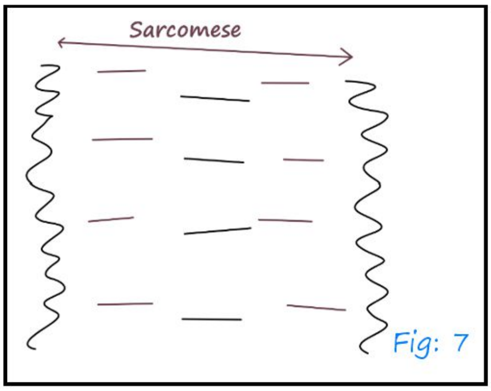


Fig: 7

- From one 2 line to other 2 line → 1 sarcomere
- A band
  - Anisotropic
  - Made up of myosin
  - Dark banal
- I band
  - Isotropic
  - Made up of actin
  - Light band
- Area which is not overlapped by actin filament
  ↓
  H band
- M line → Central bulge in myosin
- Pseudo H → light side of 2 side of M line
- During contraction
  2 Z lines will come closer
  - H band and I bind will decrease
  - A band – constant
  - M line – more prominent

Excitation – Contraction coupling 00:26:45

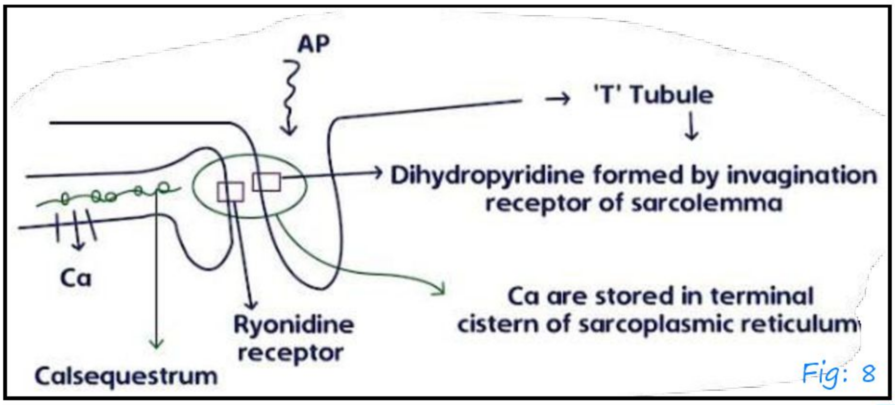

AP
→ 'T' Tubule
Dihydropyridine formed by invagination receptor of sarcolemma
Ca
Ryonidine receptor
Ca are stored in terminal cistern of sarcoplasmic reticulum
Calsequestrum

Fig: 8

When AP comes, there is taking between

dihyetropyridine and ryolnidine

↓

Calcium release

↓

Binds with troponin with

↓

Skeletal muscle contract

- SERCA – Sarcoplasmic endoplasmic reticulum calcium ATPase
- Contraction – active process
- Relaxation – active process because SERCA is needed

Sliding filament theory 00:31:04

Cross bridge cycling / sarcomere shortening

1.ATP binding

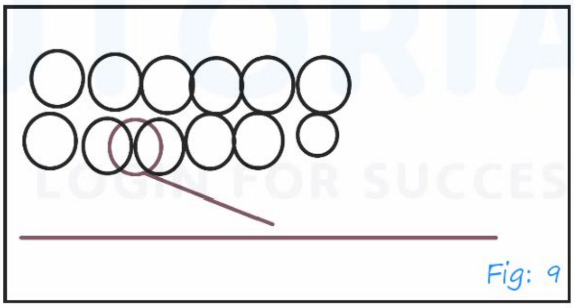


Fig: 9

- ATP binding to myosin head causes dissociation of actin – myosin complex
- When ATP comes, it will be dissociated

2.ATP hydrolysis

ATP → ADP and ip an myosin head

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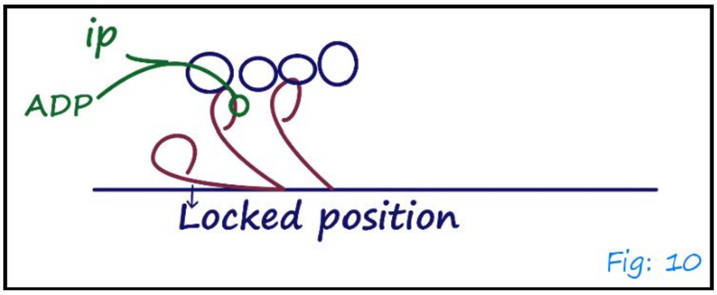

Fig: 10

- New position → cocked position is attained by ATP hydrolysis

3.When cocked position of myosin acts with actin → new position

↓↓

Cross bridge formation

4.Dissociation of ip from head of myosin

↓

Power stroke

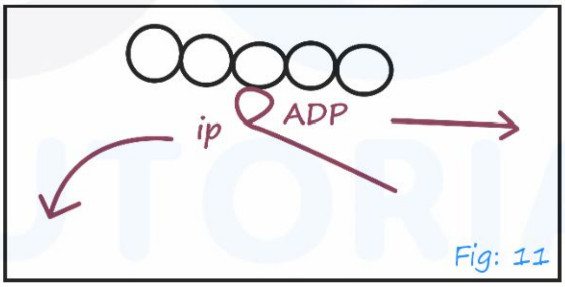

Fig: 11

5.Release of ADP

- This cycle continues until SERCA will pull calcium back to sarcoplasmic reticulum
- ATP is stopped

↓↓

Cycle stop at death

↓↓

Permanent actin myosin binding

↓↓

Rigor mortis

↓

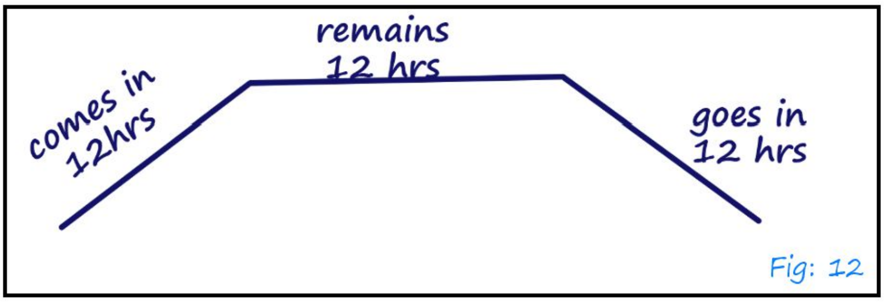

Fig: 12

- It will go because lysosome will burst and hydrolytic enzyme will eat actin and myosin

Terminologies

1.Motor unit

  - Functional contractile unit motor
  - Single spinal motor neuron + m/s fibre
  - Follows all or non-law

- Size principle → Small motor unit innervate slow twitch muscle; large motor unit innervate fast noitch muscle
- Hanemann principle
  - In large muscle contraction, small slow units are recruited first, only when required large muscles are recruited
- Maximum innervation is present in extraocular muscle → 3-6
- Less innervation → gastronomic / Back muscle

Fasciculation
↓
Involuntary contraction of single motor unit
↓
Group of ms fibre
↓
Visible grossly

Fibrillation
↓
Spontaneouces repetitive contraction of single muscle fibre due to sensitivity to acetyl choline
↓
Not visible grossly

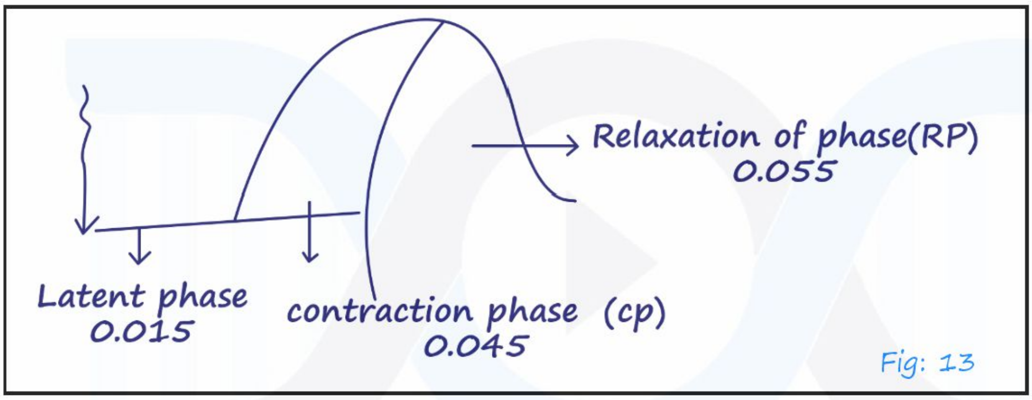

Fig: 13

- Always RP > CP
- Sustained contraction due to repeated stimuli
  ↓ Complete tetanus
  ↓ structure falls in phase of contraction
- Tetanizing frequency = 1/contraction phase

  Eg: $\frac{-10=25}{0.04}$

Frank starling law

- Force of contraction is proportional to initial length of fibre under physiological limit

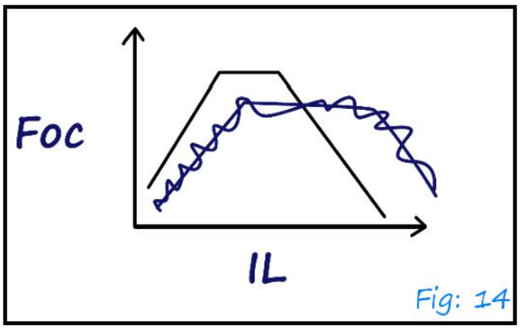

Fig: 14

Optimum length

- Minimum length of m/s fibre → maximum force of contractia
- Measure 2.25 µm
- Optimum length = resting length

Muscle contraction 00:52:12

- 2 types

Isotonic contraction	Isometric contraction
↓	↓
Contraction with same tone	Contraction when length does not change
↓	↓
Walking	pushing the wall
Bp → SBP increase and DBP decrease	Bp → SBP and DBP increase

Muscle tension 00:53:58

2 types

Active	Passive
↓	↓
- Exerted due to muscle contraction - Depends on number of cross bridges between actin and myosin - Depends on number of motor units recruited	- Exerted by elastic tissue of muscle fibre

- if we combine active and passive together → Total tension

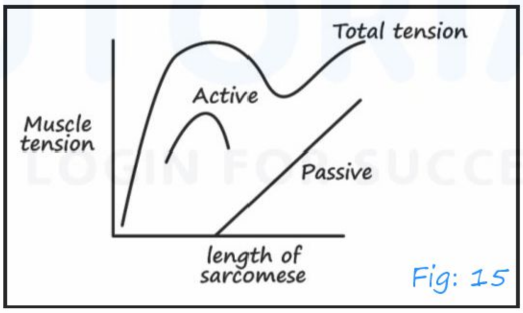

Fig: 15

Heat production 00:56:56

- Resting heat: - Heat given at rest due to basal metabolic process of muscle
- Initial heat: - Heat produced in excess of resting heat
  - 2 types
    - Activation heat → muscle contracting

  - shortening heat
- Recovery heat – Heat which is liberated by metabolism to reach into pre-contractile
- Relaxation heat
  - Isotonic contraction
  - Heat released in muscle when contraction is isotonic to restore length

---

Muscle fibres 01:00:48

- 2 types of muscle fibres
  - Slow I
  - Fast IIA and IIb

	slow	IIA	fast (IIb)
S	Slow	Fast	Fast
O	Oxidative	Oxidative	Glycolytic
R	Red	Red	White
R	Resistant To Fatigue		Fatiguable
Y			

CARDIAC AND SMOOTH MUSCLE

Cardiac muscle 00:00:30

- Striated/Involuntary
- Intercalated disc present in Z lines
- Mechanical-electrical coupling of muscle because of gap junction
- Mechanical coupling is by desmosomes
- Functional synticium – because of gap junctions
- Cannot be fatigue/tetanized
- Long refractory period
- Titin (+) for elasticity
- Mutated → Dilated cardiomyopathy
- 2 types of action potential → Pace marker & contractile

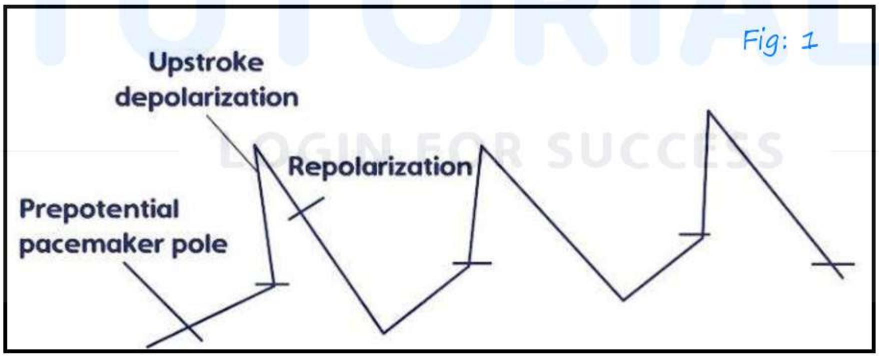
Fig: 1
Upstroke depolarization
Repolarization
Prepotential pacemaker pole

- Pre potential
  - Due to increase calcium and slow Na influx
  - Decrease eflux of K
  - HCN channel

    ↓

Hyperpolarized induced CAMP dependent channel → also called as funny leaky channel

- Depolarisation → L calcium dependent
- Repolarisation → K^+ dependent

Contractile AP

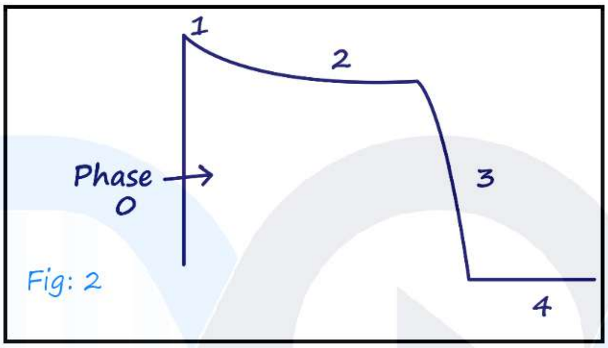

Fig: 2

Phase	0	Depolarization	influx of Na^+
	1	Early Repolarization	efflux of K^+
	2	Plateau Phase	efflux of K^+ and influx of ca^{2+}
	3	Late Repolarization	
	4	RMP	

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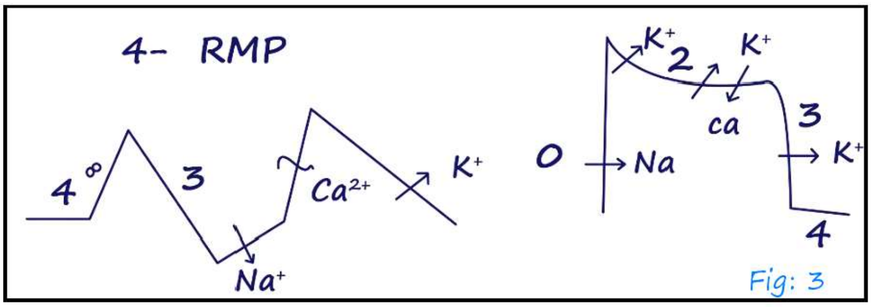

Fig: 3

Excitation contraction coupling

- Normally, AP stimulates sarcoplasmic reticulum to release calcium through DHP receptor and ryanodine receptor

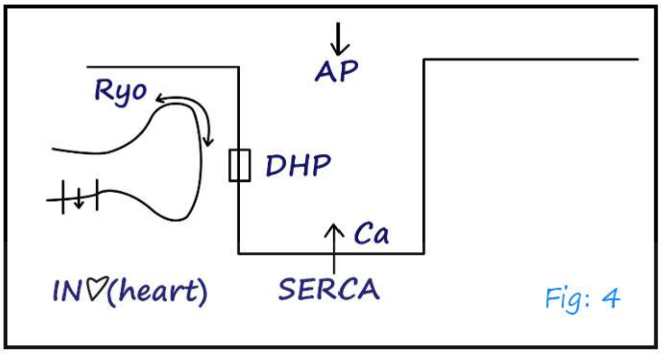

Fig: 4

In (heart)

- Along with action potential, calcium is also coming

↓↓

Induce release of more calcium

↓↓

Positive feedback mechanism

↓↓

Ca induced ca release

- Phospholamban inhibit SERCA → interfere in ca storage
- In presence of norepinephrine →

NE will inhibit phospholamban by causing phosphorylation

↓↓

Increase Ca

Muscle relaxation increase

↓↓

Positive lisitorphy

NE stimulates influence of calcium

↓↓

Ca ↑↑ → increase force of contraction → positive ionotropy

Smooth muscle

- Have less complex NMJ compared to skeletal muscle. There are no T tubules
- In place of T tubules → caveolae ⊕

  ↓

  Invagination of smooth muscle membrane
- No sarcoplasm
- No Z lines (Anchorage of actin – given by dense body)
- There are thick fibres and thin fibres, but some differences ⊕
- No troponin (Calmodulin ⊕)
- Extra proteins in smooth m/s → caldesmin and calponin → absent in skeletal muscle
- Thin filament
  - Actin
  - Tropomyosin
  - Caldesmin
  - Calmodulin
- In skeletal muscle
  - Actin
  - Tropomyosin
  - Troponin

DOC TUTORIALS
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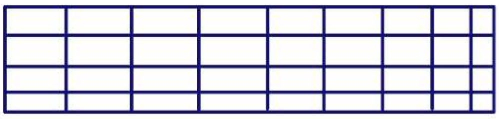
- There are 2 types of smooth muscle

Unitary / visceral	**Multiunit**
	Gap junctions absent
Due to gap junctions, they look like one	
Eg: – smooth muscle of hollow viscera	There are in intraocular muscle vas deferens ciliaris

Contraction of Smooth muscle

- Calcium comes from ECF and binds with calmodulin

Activation of calmodulin depend MLCK

↓

Myosin light chain kinase

↓

Phosphorylation of myosin head

↓

Contraction

- For relaxation, you need to dephosphorylate myosin

→ MLCP → myosin light chain phosphatase

MLCP

Relaxation

Sustained contraction

↓

Plasticity

↓

Explained by LATCH mechanism

↓

Strain in the muscle even after dephosphorylation (Cross bridge continues with minimal ATP)

SYNAPSE

- This term synapse is given by Sherrington.
- 2 types

i. Electrical

ii. chemical

Electrical	Chemical
• Because of gap junction	• Because of pre synaptic vesicles
• Ion current	• Chemical transmission
• Cytoplasmic continuity present	• Absent
• Bidirectional	• Always unidirectional
• Synaptic cleft 4 nm	• 20-40 nm

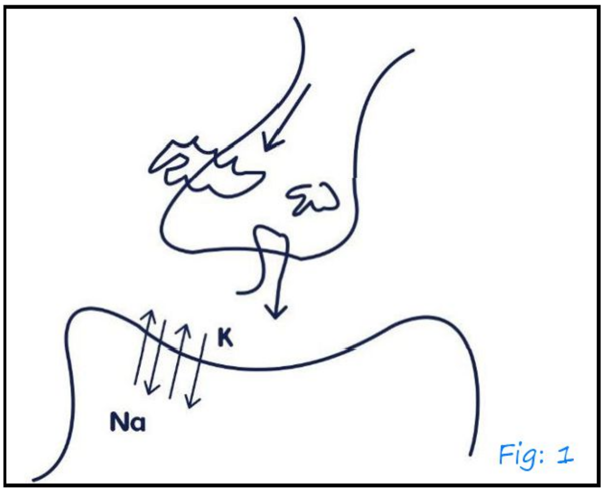
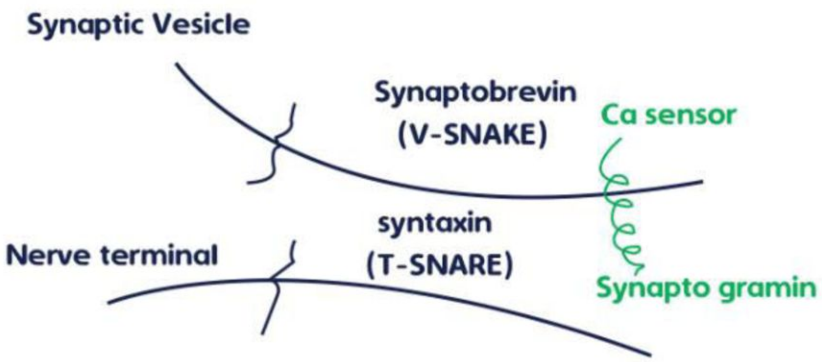
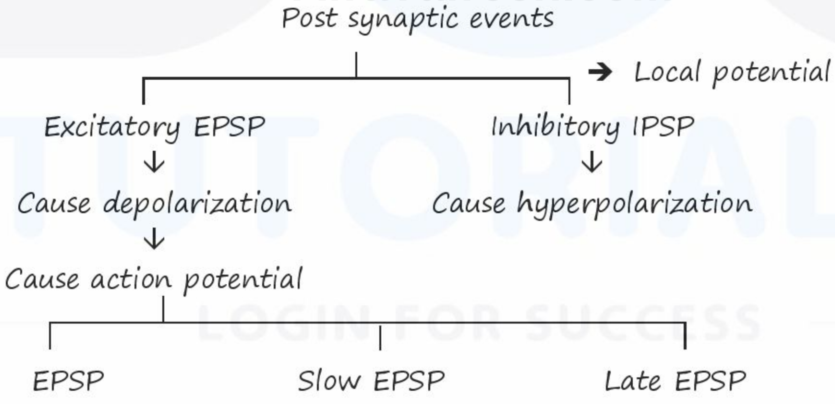


Fig: 1


Synaptic Vesicle
Synaptobrevin (V-SNAKE)
Ca sensor
syntaxin (T-SNARE)
Nerve terminal
Synapto gramin

- Synaptic vesicle, nerve terminal, synaptobrevin (v-SNARE), syntaxin(T-SNARE),

- Synapto brevin] - important for docking phenomenon
  Syntaxin]
- Synaptogramin – acts like a calcium sensor


Post synaptic events
→ Local potential
Excitatory EPSP
Inhibitory IPSP
Cause depolarization
Cause hyperpolarization
Cause action potential
EPSP
Slow EPSP
Late EPSP

- EPSP → due to influx of Na/Ca
  → happen everywhere
- Slow EPSP → Decreases K efflux
  → found in – autonomic ganglion
  - Cardiac muscle
  - Smooth muscle
  - Cortical neuron

- Late EPSP → decreases K efflux
  → Found in sympathetic ganglion
- IPSP – due to Cl^- influx
- Slow IPSP – Increases K – efflux
  - Occurs in – autonomic ganglion
    - Heart

2 types of inhibition

i. If you have neuron A and inhibits neuron B

↓

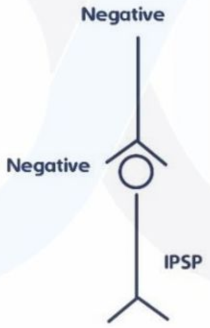
Post synaptic inhibition

E.g. Strychinine

Inhibits post synaptic inhibition→

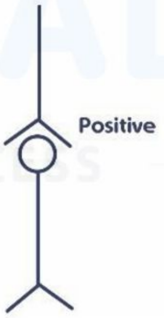
By antagonizing action of

Glycine in spinal cord.



ii. Pre synaptic inhibition

- IPSP inhibits pre synaptically
- Positive inhibition



Nerve cell

Neurons	Glial cells
↓ After birth, neurons cannot be generated	- 10 times neuron - Can be formed after birth

Glial cells 2 types

Microglial ↓ Phagocytosis

Macroglial ↓ 3 types

i. Astrocytes
  - Tropic to neuron
  - Release growth factor
  - Regulate permeability of BBB

Astrocyte 2 types – Fibrous → found in white matter

Protoplasmic → grey matter

ii. Oligodendrocytes
iii. Schwann

→ Both cause myelination

- Oligodendrocytes – myelination of CNS
- Schwan – myelination of PNS

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- 1 cell can cause myelination of multiple neurons

↓

E.g. Multiple sclerosis

Defect in oligodendrocytes

- 1 cell causes myelination of single neuron

↓

E.g. GBS

Defect in schwann cell

- c/s of peripheral nerve → lot of fasciculus → have axons with myelin sheath.

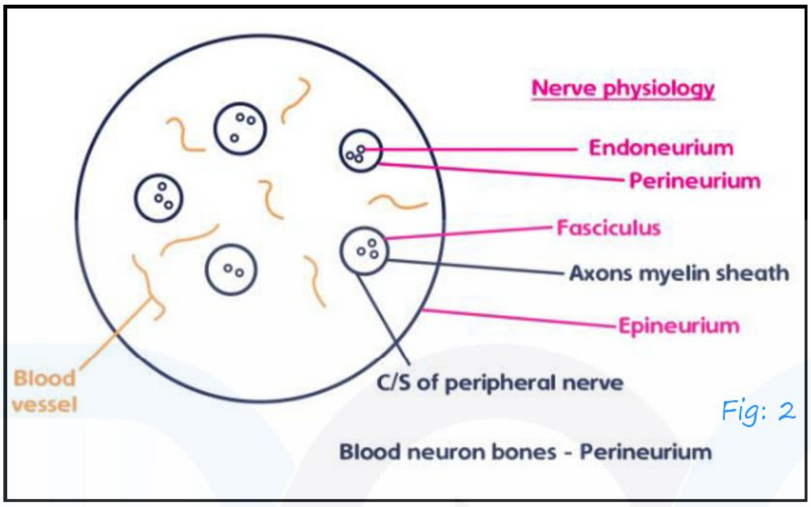
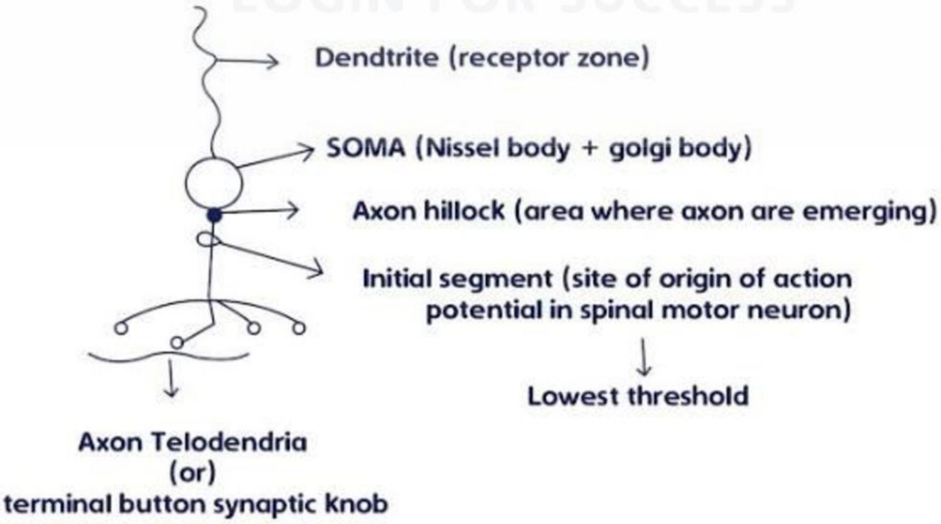

Nerve physiology
Endoneurium
Perineurium
Fasciculus
Axons myelin sheath
Epineurium
Blood vessel
C/S of peripheral nerve
Blood neuron bones - Perineurium

Fig: 2

- Inner most is endoneurium
- Middle → perineurium
- Outer most – epineurium
- Blood vessels are present inside
- Blood neurons are formed by perineurium


Dendtrite (receptor zone)
SOMA (Nissel body + golgi body)
Axon hillock (area where axon are emerging)
Initial segment (site of origin of action potential in spinal motor neuron)
Lowest threshold
Axon Telodendria
(or)
terminal button synaptic knob

- 1st site of origin of action potential in cutaneous sensory neuron – initial node of Ranvier

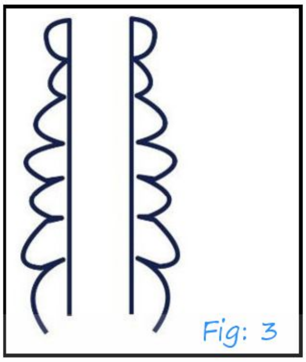


Fig: 3

Types of Neurons

i. Unipolar → there is no clear cut demarcation between dendria/axon

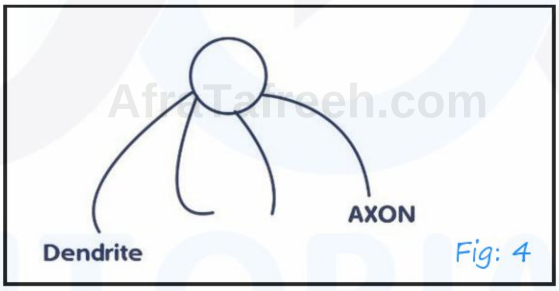


Fig: 4

E.g. Mesencephalic nucleus of V nerve

ii. Pseudo unipolar → Bipolar subclass actually

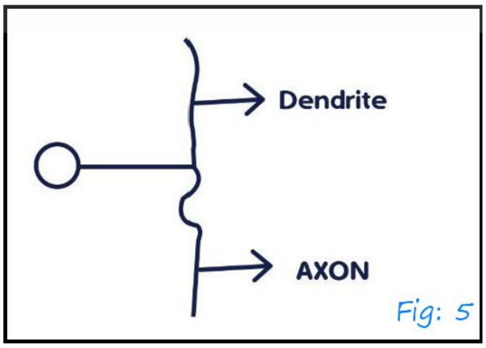


Fig: 5

E.g. Dorsal root ganglion nerve (sensory neuron)

iii. Bipolar neuron → distinguish dendrite and axon

Dendrite → take information to the cell

Axon → take information from the cell & retina, olfactory epithelium), sensory ganglion of cochlear and vestibular nerve.

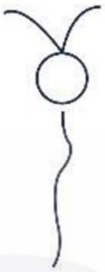
iv. Multipolar

- One axon
- Multiple dendrite

E.g. Motor neuron

Hippocampal pyramidal cell

Cerebellar purkinjee cell



Axon transport 00:28:00

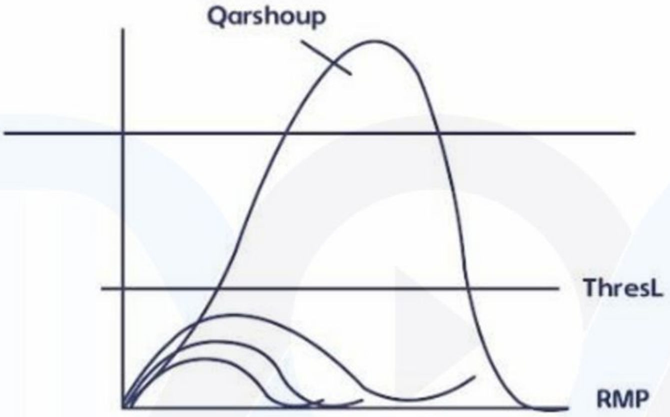
- Can be Slow/Fast
  - Fast 400 mm/day
    - Orthograde/anterograde ↓ Due to kinesin
      - Nutrition Transport
      - Enzymes
      - Neurotransmitter Transport
    - Retrograde ↓ Due to dynein ↓ Kartagener's syndrome
      - Tetanus toxin
      - nerve growth factor
      - virus (rabies)
  - Slow 0.5 to 10 mm /day ↓
    - Always anterograde ↓ Triad of Kartagener syndrome
      - chronic sinusitis
      - Bronchiectasis
      - Situs inversus

Slow

- Always antegrade
- Needs cytoskeleton –
  - – Microtubule
  - – Actin content misorganized

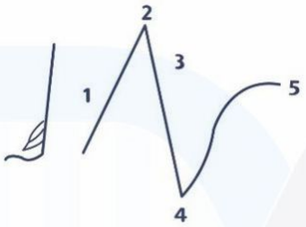
↓

Transports pf soluble protein



- Note: puffer fish–tetrodoxin-block voltage gated sodium channel

AP

Biphasic Ap	Compound AP
Both recoding electrodes are on the surface only	When nerve bundle is stimulated /stimulating more than one axon ↓ Combination of all potentials
	
• Follows all or one law • upward deflection & downward deflection	• Not following all or one law • Multipeaked action potential

Nerve fiber classification 00:38:09

- 2 types
  - Erlanger & gaser → A,B, C is used for sensory, motor& ANS
  - Numerical → I, II III, IV → only for sensory nerve

- A } myelinated
- B } myelinated
- C → unmyelinated

speed decrease from A to C

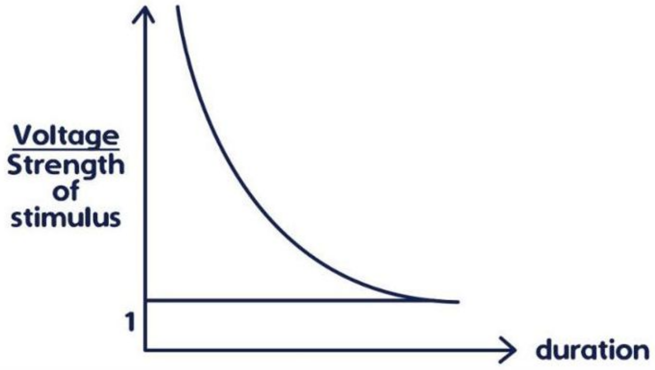
- A- α → equalent to 1a / 1b → proprioception
  → somatic motor

β	II	Touch & pressure
γ	–	Efferent to muscle Spindale
delta	III	Pain, temperature (cold) (fast pain)
B	–	Preganglionic autonomic nerve
C	IV	– Slow Pain & temperature – Post ganglion

- Speed will decrease from A to C
  - Maximum speed – A
  - Minimum speed _ C
- Therefore, Spike duration – maximum for C

  C > B > A
- ARP → C > B > A

Strength & duration



↓

- Rheobase → minimum strength of current to get action potential
- Utilization time → time taken by Rheobase
- Chronaxie – time taken by current
- Which is double of Rheobase
- Chronaxie A < B < C

  ↓ ↓

  Minimum chronaxie maximum (since minimum speed)
- More is the chronaxie → lesser the excitability
- Lesser Is the chronaxie → more excitability
- Aα > Aβ > Aγ > A delta > B> C

Susceptibility of Neuron

- Pressure A> B > C
- Hypoxia B > A > C
- L A → Aγ & A delta > A α > A β > B> C

Nerve injury 00:53:50

Seddon classification

- Neurapraxia: - nerve compression injury
  - Axon is intact
  - Local myelin injury
  - Motor affected > sensory
  - Recovery hours to month
- Axonotmesis - Axons + myelin sheath involved
  - Conduction failure
  - Wallerian denegation due to loss of axoplasm (anterograde degeneration)

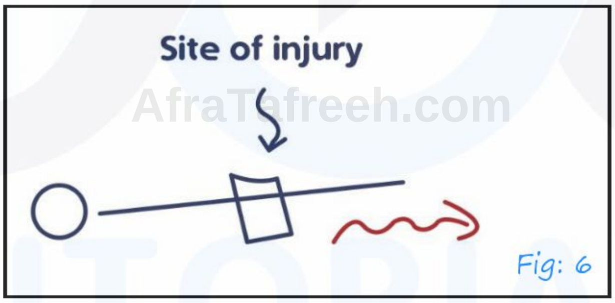


Fig: 6

- [Proximal to site of injury → retrograde degeneration]

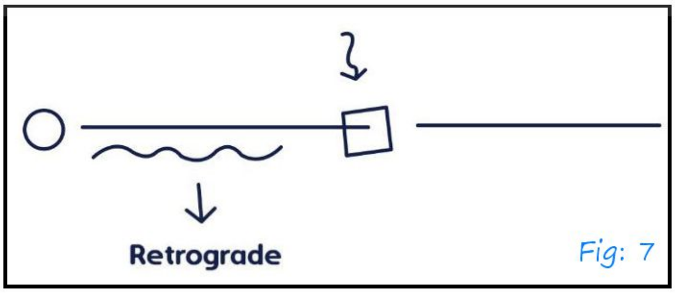


Fig: 7

- Recovery of axontemesis → weeks to months
- Neurotemies – Nerve transection

- Axon + interruption of connective tissue
- Most severe form
- Recovery is always incompetent

Sunderland classification

- 1st degree – neuropraxia
- 2nd degree – axontemesis
- 3rd degree – axontemesis + damage to endoneurium
- 4th degree – axontemesis + endoneurium + perineurium,
- 5th degree – neurotemesis

Changes

- Myelin sheath degenerative
- Swelling of cell body
- Nucleus goes to eccentric position
- RER is fragmented → chromatolytic reaction
- Nerve regrows with multiple branches

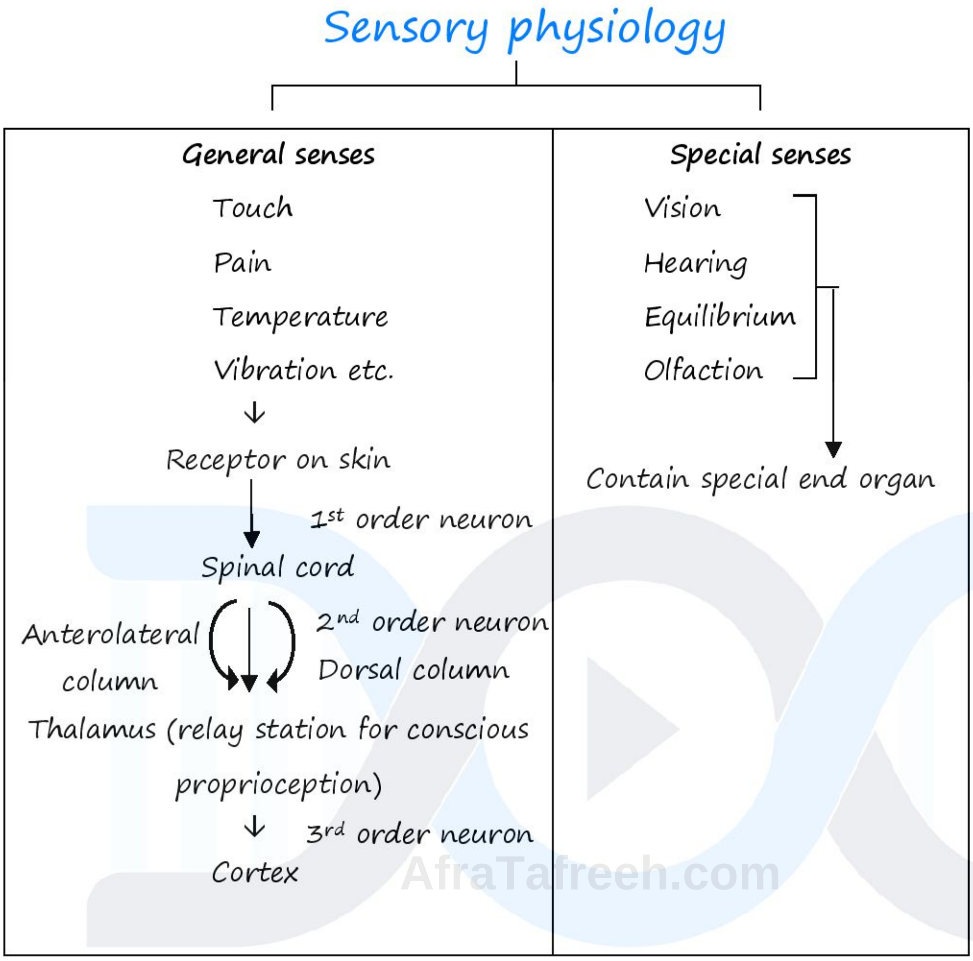
  ↓

  Sprouting
- If nerve is cut → skeletal muscle becomes sensitive to acetyl choline

  ↓

  Hypersensitivity denervation

SENSORY RECEPTOR


Sensory physiology
General senses
Touch
Pain
Temperature
Vibration etc.
Receptor on skin
1st order neuron
Spinal cord
2nd order neuron
Anterolateral column
Dorsal column
Thalamus (relay station for conscious proprioception)
3rd order neuron
Cortex
Special senses
Vision
Hearing
Equilibrium
Olfaction
Contain special end organ

Cutaneous Receptors 00:05:45

i. Mechano – Receptor

- Tactile receptor
    - Touch
    - Pressure
- Nociceptor
- Proprioceptors
    - Muscle spindle
    - Golgi tendon organ
    - Joint capsules

ii. Thermoreceptors

- Cold: A delta
- Warm: Type C fibers

Transient receptor potential M (TRPM)

- Menthol
- Cold receptor

TRP-V

- Vanelloid
- Hot sense.

iii. Chemoreceptors: Smell/Taste/Osmoreceptors (in hypothalamus)

iv. Photoreceptor: Telo receptor/ electromagnetic receptor

- Rod
- cones

v. Polymodel – NOCI receptor

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Properties of Receptor 00:10:50

M	L	I	D
Modality ↓ Touch pain Temperature	Location ↓ - Important for receptive field size - Area of skin from where receptors collect information - Receptor density ↓	Intensity Amplitude of stimulus constant ↓ They follow all/ none law	Duration Time between start & end of stimulus

It is basis for two point discrimination - Smaller size → better two point discrimination Shortest: (lips/ finger tips) (1-2 mm) Greatest: Back (50-60 mm) - It also depends on cortical representation ↓ Larger the representation in cortex better is two point discrimination It is important for texture determination.	More frequency of stimulation ↓ Increases intensity	Less frequency of stimulation ↓ Decreases intensity

Tactile Receptor 00:18:45

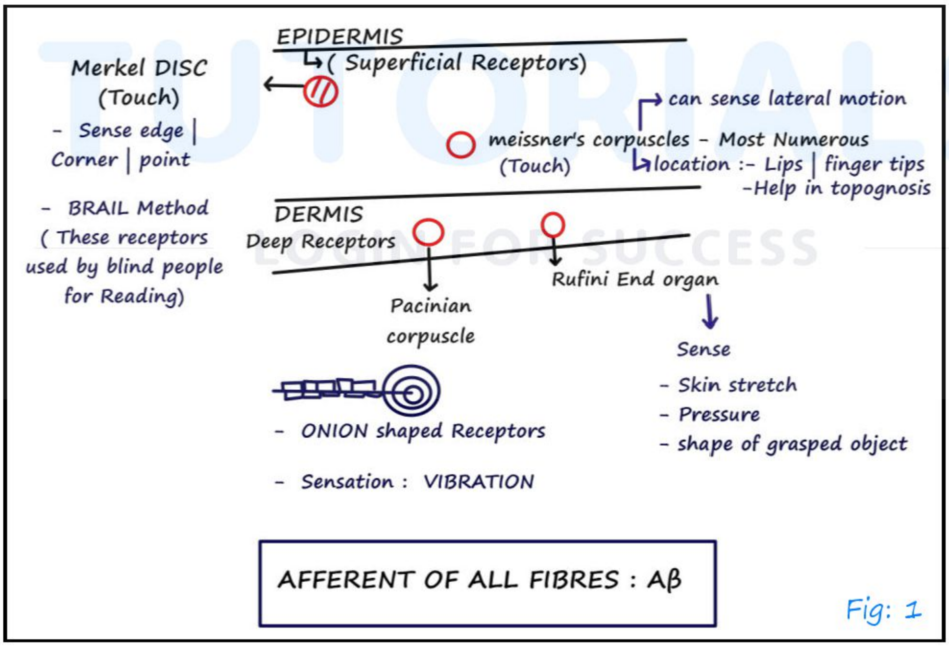

EPIDERMIS
↳(Superficial Receptors)
Merkel DISC
(Touch)
- Sense edge | Corner | point
- BRAIL Method
(These receptors used by blind people for Reading)
can sense lateral motion
meissner's corpuscles - Most Numerous
(Touch)
location :- Lips | finger tips
-Help in topognosis
DERMIS
Deep Receptors
Pacinian corpuscle
Rufini End organ
Sense
- Skin stretch
- Pressure
- shape of grasped object
- ONION shaped Receptors
- Sensation : VIBRATION
AFFERENT OF ALL FIBRES : Aβ

Fig: 1

Afferent of all fibres: A β

- Rapid adapting A/K/A phasic Receptors
  - Meissners Corpuscle
  - Paccinian corpuscle
- Slow Adapting A/K/A Tonic receptors
  - Merkel disc
  - Free nerve endings (pain)
  - Ruffini end organ

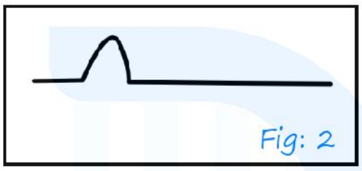


Fig: 2

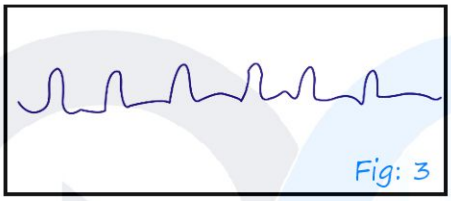


Fig: 3

Nociceptor (Pain) 00:30:25

Free nerve ending

They are voltage gated sodium channel (- Absence of these receptors leads → congenital insensitivity to pain syndrome)

Two types of afferent fibres

A delta

- Myelinated
- Fast pain / first pain
- Good pain
  ↓
  since, help in preventing complex injuries
- Sharp pain
  ↓
  localization present
  &
  intensity of stimulus can be known
- Neurotransmitter
  ↓
  glutamate

C fibres

- Unmyelinated
- Slow pain / second pain
- Bad pain (Psychological)
- Dull pain / visceral pain / chronic pain / burning pain
- Neurotransmitter
  ↓
  substance P

Note

Algogen: Substances which decrease pain threshold (Hyperalgesia) and

↓ increase intensity of pain

Pain (stimulate free nerve endings)

Example:

- Inflammatory products
- Histamine
- Prostaglandin
- Substance P
- Serotonin
- Bradykinin – most potent algogen

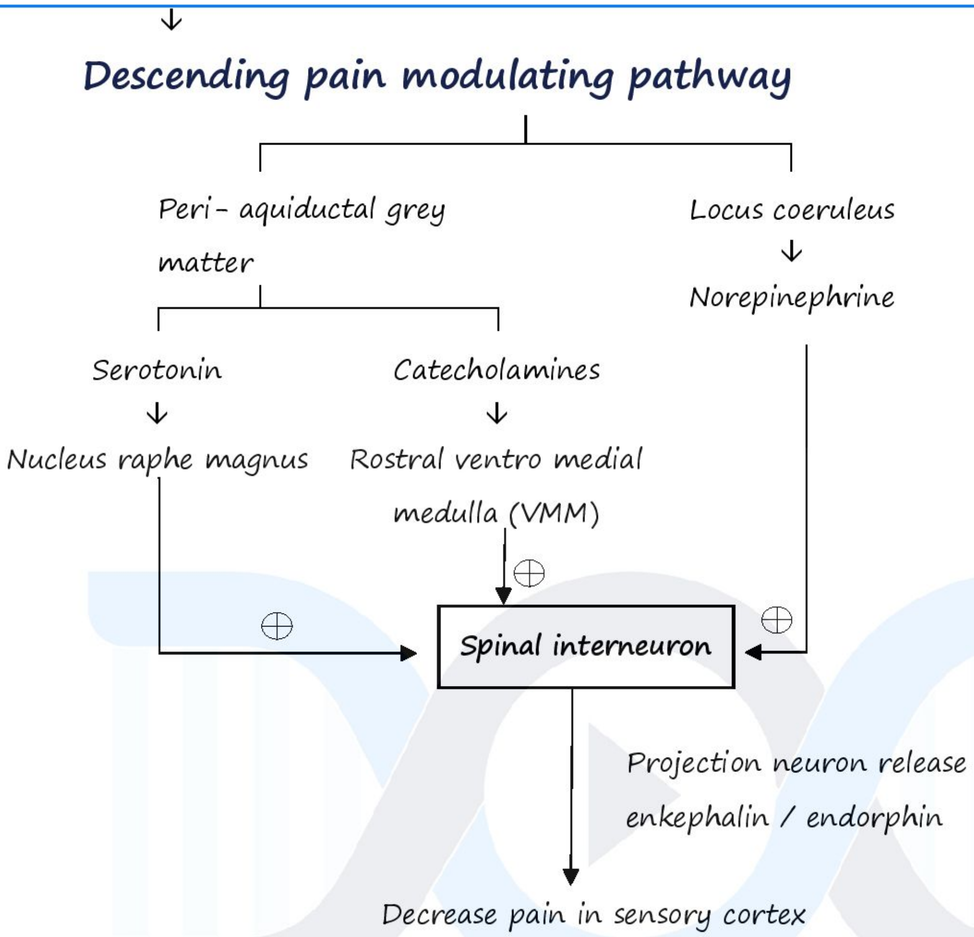
Allodynia: When non painful stimulus causes pain

Poly model since, Pain and temperature
- TRP V_1 (Vanelloid → Capsicum / H^+ / temperature >43°c
- TRP V_2 → Temperature >52°c

Normal body temperature
- TRP V_3 → Temperature > 35°c
- TRP V_4 → Temperature > 27°c Therefore, Normally $TRPV_4$ > $TRPV_3$

Cold
- TRP M_8 → Menthol (8 to 28°c)
- TRP A → lower temperature (<17°c) (A Ankyrm)

Analgesic pathway 00:43:30


↓
Descending pain modulating pathway
Peri- aquiductal grey matter
Locus coeruleus
↓
Norepinephrine
Serotonin
Catecholamines
↓
↓
Nucleus raphe magnus
Rostral ventro medial medulla (VMM)
⊕
⊕
⊕
Spinal interneuron
Projection neuron release enkephalin / endorphin
Decrease pain in sensory cortex

Modulation of pain 00:48:00

- Melzalk and wall theory – gate control mechanism

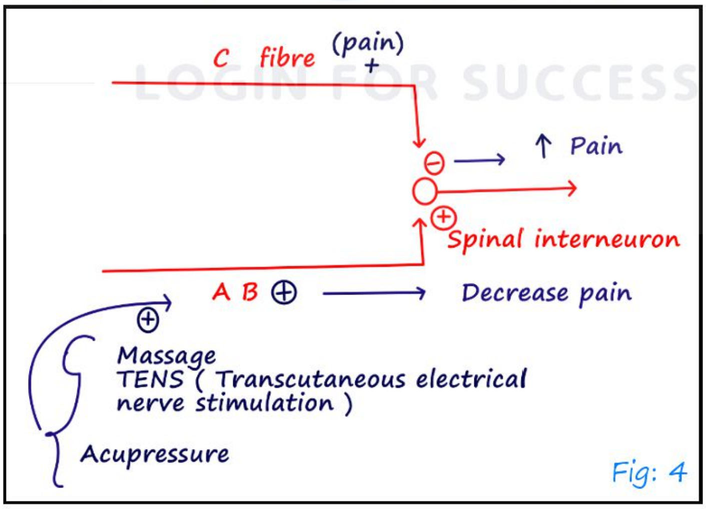

C fibre
(pain)
+
⊖
↑ Pain
⊕
Spinal interneuron
A B ⊕
Decrease pain
⊕
Massage
TENS (Transcutaneous electrical nerve stimulation)
Acupressure

Fig: 4

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SOMATOSENSORY PATHWAY

Aδ / C →
Aβ →
Receptor → Spinal cord → Thalamus → Sensory cortex.

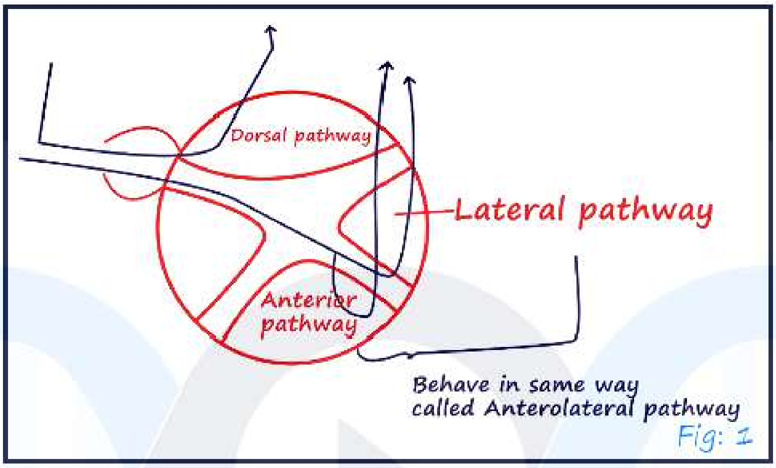
Dorsal pathway
Lateral pathway
Anterior pathway
Behave in same way called Anterolateral pathway

Fig: 1

DOT TUTORIALS
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Dorsal

- Heavily myelinated
- fast pathway
- Two-point discrimination
- vibration
  proprioception
- fine touch
- stereognosis
- Crosses in medulla

Anterolateral

less myelinated
↓
Slow

Anterior

Crude touch
↓
Itch/tickling
sexual sensation

Lateral

pain and temperature

- Cross in spinal cord

Dorsal Pathway 00:06:18

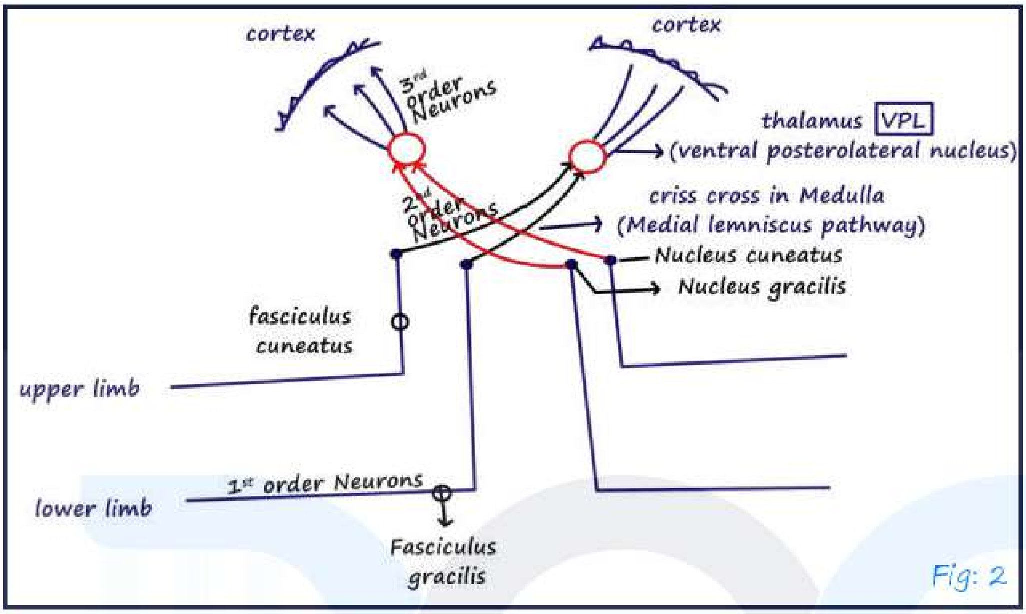
cortex
cortex
3rd order Neurons
thalamus VPL
→(ventral posterolateral nucleus)
2nd order Neurons
criss cross in Medulla
→ (Medial lemniscus pathway)
Nucleus cuneatus
Nucleus gracilis
fasciculus cuneatus
upper limb
lower limb
1st order Neurons
Fasciculus gracilis

Fig: 2

VPL – Infarction

↓

Thalamic pain syndrome

Anterolateral pathway 00:10:40

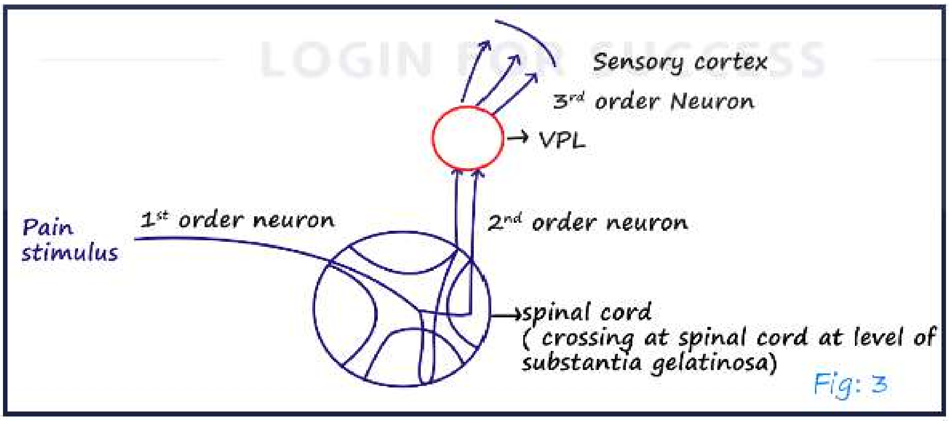
Sensory cortex
3rd order Neuron
→ VPL
Pain stimulus
1st order neuron
2nd order neuron
→spiral cord
(crossing at spinal cord at level of substantia gelatinosa)

Fig: 3

Sensory cortex 00:12:20

- Sensory cortex important for localization of sensory stimulus

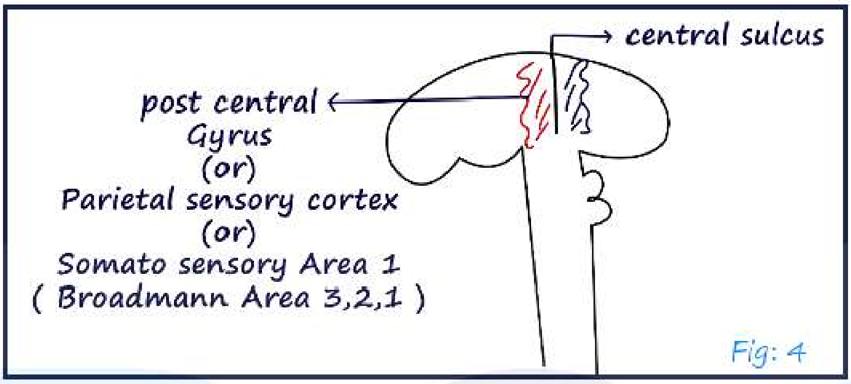
central sulcus
post central
Gyrus
(or)
Parietal sensory cortex
(or)
Somato sensory Area 1
(Broadmann Area 3,2,1)

Fig: 4

Somatosensory area II

Broadman area 5,6,7

↓

Concerned with analysis of touch (sterognosis)

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Sensory homunculus

- Vertical arrangement of body parts
- Inverted representation

Top → Leg
Bottom → Face
Medial → leg
Lateral → Face

Representation based on usage of body parts
Maximum representation → Lips / thumbs
Minimum representation → Trunks + Hips

No visceral organ representation in sensory cortex

↓

Therefore, we have referred pain from visceral organs

Brown Sequard syndrome

- Functional hemi section of spinal cord

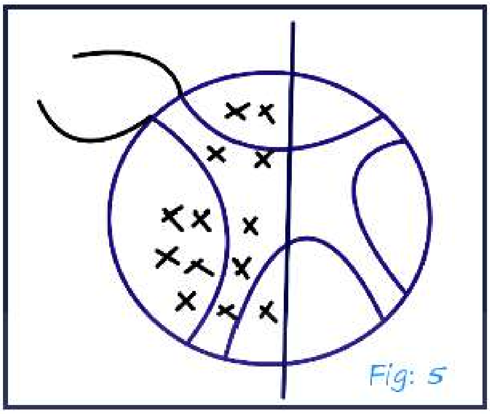

Fig: 5

1. Ipsilateral loss of dorsal column pathway
2. Contralateral loss of anterolateral pathway – Pain and temperature
3. Ipsilateral loss of descending motor pathway

Laws of sensory physiology 00:21:22

1. Muller's law: Law of specific nerve energy

   Pathways and receptors are specific for particular stimulus

2. Weber Fechner law:

   Magnitude of sensations felt ∝ log of intensity of stimulus

3. Bell magendie law:

   Dorsal roots of spinal cord → sensory

   (Ventral roots are motor)

4. Law of projections: Phantom limb pain

Syringomyelia

- Associated with Arnold chiari Type 1 malformation
- Cerebellar tonsils are pushed down into foramen magnum than into spinal cord → Leading to dissociative sensory loss

  ↓

  Loss of pain and temperature with sparing of touch and vibration.

SOMATOSENSORY PATHWAY

Aδ / C → Receptor → Spinal cord → Thalamus → Sensory cortex.

Aβ → Receptor

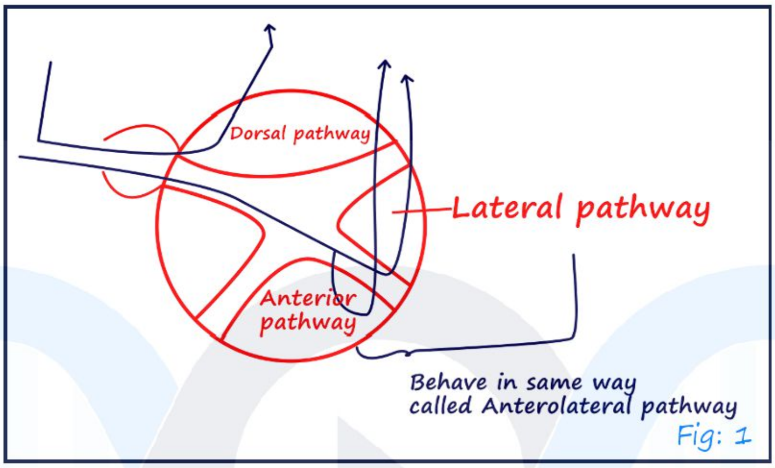
Dorsal pathway
Lateral pathway
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Fig: 1

Dorsal

- Heavily myelinated
- fast pathway
- Two-point discrimination
- vibration proprioception
- fine touch
- stereognosis
- Crosses in medulla

Anterolateral

less myelinated

↓

Slow

Anterior

Crude touch

↓

Itch/tickling

sexual sensation

- Cross in spinal cord

Lateral

pain and temperature

Dorsal Pathway 00:06:18

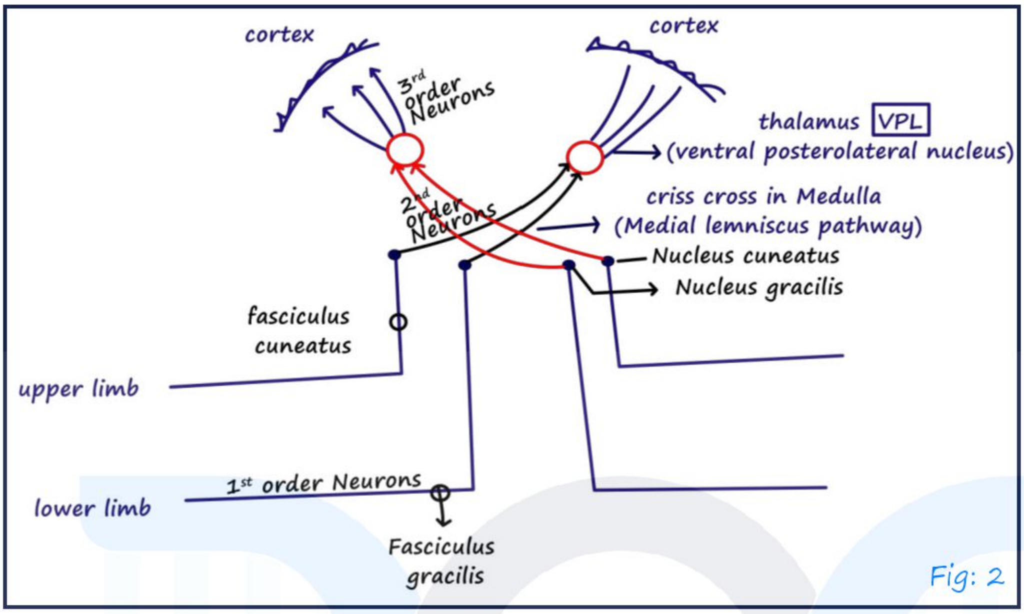
cortex
cortex
3rd order Neurons
thalamus VPL
(ventral posterolateral nucleus)
criss cross in Medulla
(Medial lemniscus pathway)
2nd order Neurons
Nucleus cuneatus
Nucleus gracilis
fasciculus cuneatus
upper limb
1st order Neurons
lower limb
Fasciculus gracilis

Fig: 2

VPL – Infarction

↓

Thalamic pain syndrome

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Anterolateral pathway 00:10:40

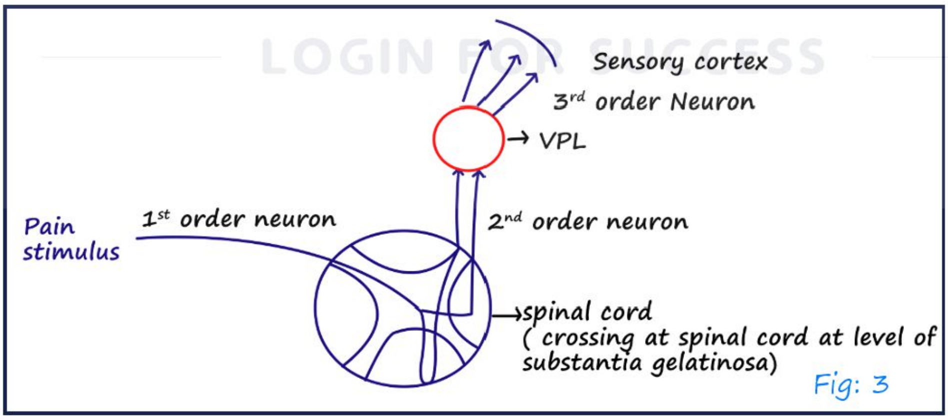

Sensory cortex
3rd order Neuron
VPL
Pain stimulus
1st order neuron
2nd order neuron
spinal cord
(crossing at spinal cord at level of substantia gelatinosa)

Fig: 3

Sensory cortex 00:12:20

- Sensory cortex important for localization of sensory stimulus

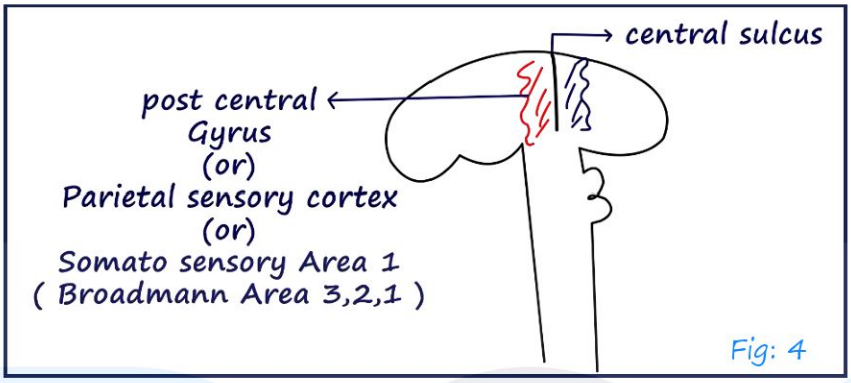

central sulcus
post central
Gyrus
(or)
Parietal sensory cortex
(or)
Somato sensory Area 1
(Broadmann Area 3,2,1)

Fig: 4

Somatosensory area II

Broadman area 5,6,7

↓

Concerned with analysis of touch (sterognosis)

Sensory homunculus

- Vertical arrangement of body parts
- Inverted representation

Top → Leg
Bottom → Face
Medial → leg
Lateral → Face

Representation based on usage of body parts
Maximum representation → Lips / thumbs
Minimum representation → Trunks + Hips

No visceral organ representation in sensory cortex

↓

Therefore, we have referred pain from visceral organs

Brown Sequard syndrome

- Functional hemi section of spinal cord

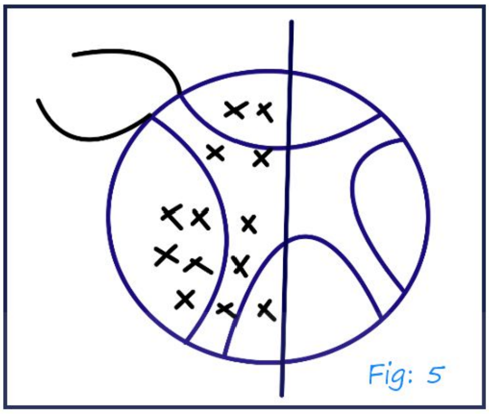


Fig: 5

1. Ipsilateral loss of dorsal column pathway
2. Contralateral loss of anterolateral pathway – Pain and temperature
3. Ipsilateral loss of descending motor pathway

Laws of sensory physiology 00:21:22

1. Muller's law: Law of specific nerve energy

   Pathways and receptors are specific for particular stimulus

2. Weber Fechner law:

   Magnitude of sensations felt ∝ log of intensity of stimulus

3. Bell magendie law:

   Dorsal roots of spinal cord → sensory

   (Ventral roots are motor)

4. Law of projections: Phantom limb pain

Syringomyelia

- Associated with Arnold chiari Type 1 malformation
- Cerebellar tonsils are pushed down into foramen magnum than into spinal cord → Leading to dissociative sensory loss

↓

Loss of pain and temperature with sparing of touch and vibration.

VISION

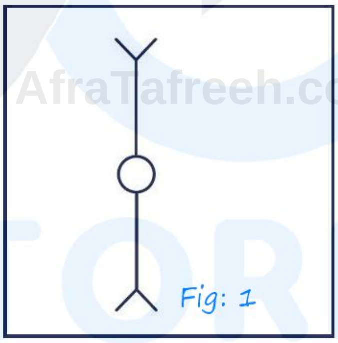
Retina → Lateral geniculate body → Visual cortex
↓
7 cells

1st order neurons

1. Rods – Night vision / Extra Foveal / Rhodopsin
2. Cones – Day vision / Fovea / Iodopsin

2nd order neurons

3. Bipolar cells –



- Connect rods and cones with ganglion cells

3rd order neurons

4. Ganglion cells
   - Only cell in retina with action potential
   - Only cell – output of retina
   - Axon of optic nerve
5. Horizontal cells
   - Connect rods with cones

6.Amacrine cells

- Connects ganglion cells with bipolar cells
- Releases acetyl choline

7.Muller cell

- Supporting cell
- No role in visual processing
- Blood retina barrier

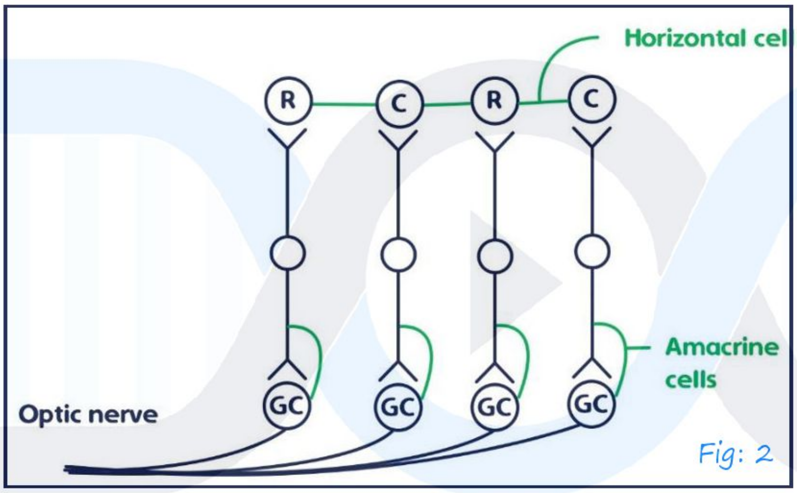

Horizontal cell
R
C
R
C
Amacrine cells
Optic nerve
GC
GC
GC
GC

Fig: 2

Order of neurons

- 1st – Rods and cones
- 2nd – Bipolar cells
- 3rd – Ganglion cells
- 4th – Lateral geniculate body
- 5th – visual cortex

Direction of stimulation

In dark

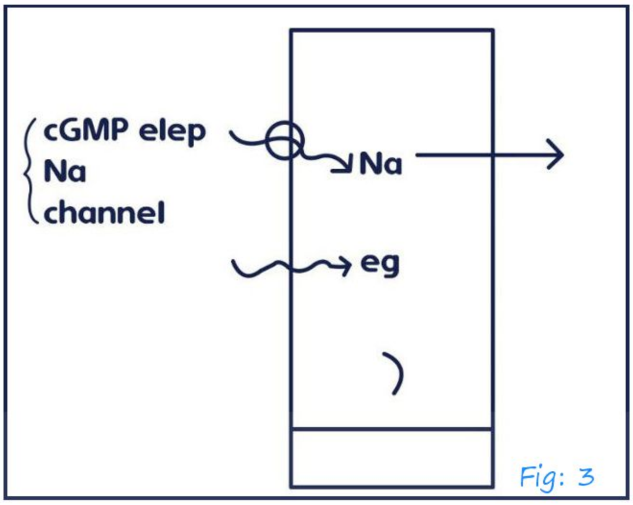


Fig: 3

cGMP dependent Na channel open → Increase Dark sodium current → Depolarization → Calcium influx → increase Glutamate

In light

Light
↓↓↓
Cis Retinol ⟶ Transretinol
Activate
⊖ ↓ Activate
Sildenafil (PDI) → Phosphodiesterase ← Transducin
↓ ↓
CGMP → GMP (G Protein coupled Receptor)
↓ cGMP
cGMP dependent Na channels – closed
↓↓
Na influx stopped
↓↓
Hyperpolarization

- Release of glutamate decrease

C is Retinal

↓

B – Bathmorhodopsin

L – Lumirhodopsin

M – Meta rhodopsin – I

↓

Meta rhodopsin – II

↓

Trans retinol

Lateral geniculate body

- 6 layers

  1,2 → Magnocellular layer → movement of eyeball

  3,4,5,6 → Parvocellular layer → color vision processing

  Layer 2,3,5 → Receive input from I/L eye

  Layer 1,4,6 → Receive input from C/L eye

  LGB → Visual cortex (Occiput)

  ↓

  Also known as calcarine cortex (Broadman's Area 17,18,19)

  - More myelinate
  - Striations of genneri

- Cells of visual cortex
  - Simple ⎤ Detects feature
  - Complex ⎦
  - Blobs → colour vision

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Colour vision pathway

- Retina cones → Thalamus (LGB) → cortex (Blobs)
  ↓
  Parvocellular layer

Cones

- L cones – Red $\overset{\ominus}{\rightarrow}$ Protanopia
- S cones – blue $\overset{\ominus}{\rightarrow}$ Tritanopia
- M cones – green $\overset{\ominus}{\rightarrow}$ Deuteronopia
  Most common → Red/Green defect (X linked Recessive)
  ↓
  Female carriers
  Males affected

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Cortex

- Occipital cortex also known as striate cortex
- Parietal
  ↓
  Dorsal pathway
  ↓
  Extra ocular movement
- Temporal
  ↓
  Ventral pathway
  ↓
  Colour vision
- Parietal, Temporal – Extra striate cortex

- Meyer's loop – Temporal cortex visual fibre

- Baumi loop – Parietal cortex visual fibre
- Inferior temporal cortex = face identification

  ↓

  Lesion → Prosopagonosia

The fibers from contralateral nasal retina project to the following layers of lateral geniculate nucleus

a. 2,3,5
b. 1,2,3
c. 1,4,6
d. 4,5,6

The rod receptor potential differs from other surface receptors in that it shows

a. Depolarization
b. Decreased negativity
c. Increased conductance of sodium
d. Hyperpolariza

The only neurons in retina showing action potential are

a. Bipolar cells
b. Ganglion cells
c. Amacrine cells
d. Rods and cones

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Amacrine cells secrete

a. Acetylcholine
b. Serotonin
c. Histamine
d. Glutamate

HEARING, OLFACTION AND TASTE

EAR 00:00:11

EAR

- Hearing → Cochlea
- Balance → vestibular apparatus

Cochlea

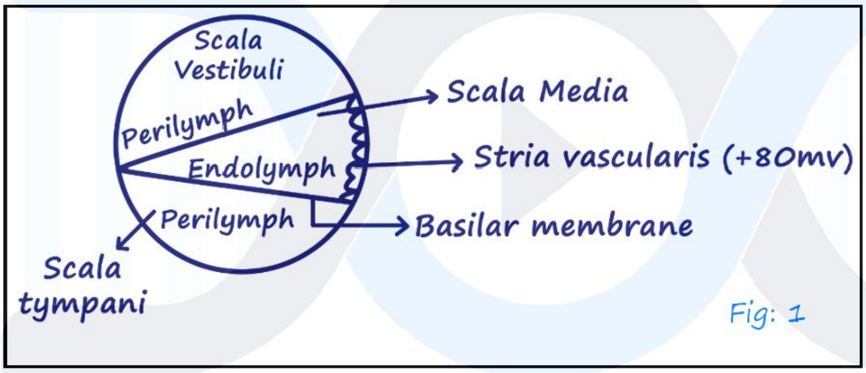
Scala Vestibuli
Perilymph
Endolymph
Perilymph
Scala tympani
Scala Media
Stria vascularis (+80mv)
Basilar membrane

Fig: 1

Organ of corti

Hair cell

Outer hair cell	Inner hair cell
• More in number less innervated	• Less in number but max. Innervated

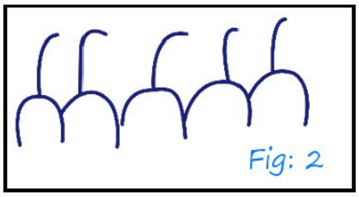

Fig: 2

Outer Hair Cell

- Ototoxic drug (aminoglycosides) damages

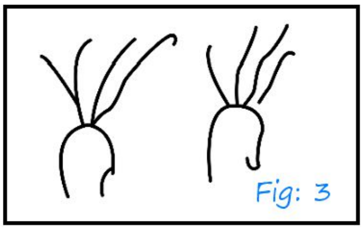

Fig: 3

Inner Hair Cell

Dieter cells → supporting cells

- Bending towards tallest one

  ↓

  Depolarization

  ↓

  Entry of K^+ ions

  ↓

  K – current

  ↓

  Oto-Acoustic emission

  (OAE/KEMP waves)

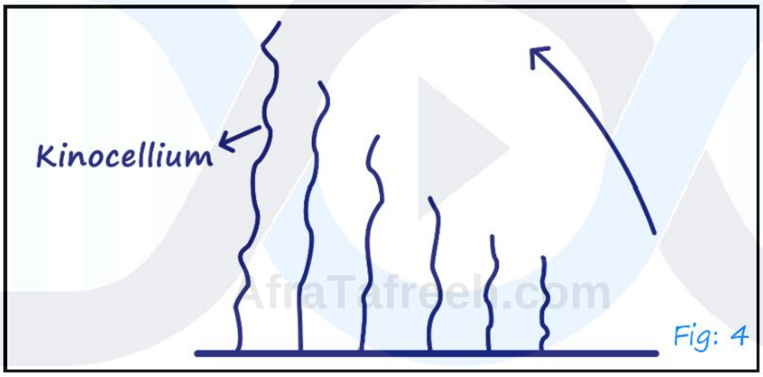

Fig: 4

- Bending away from tallest

  ↓

  Hyperpolarization

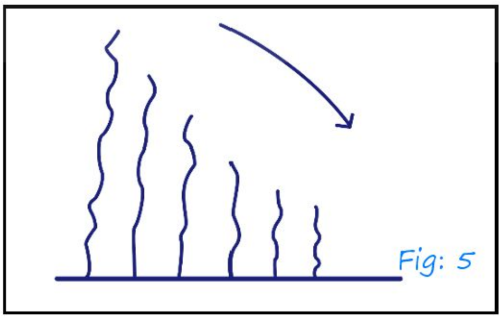

Fig: 5

Auditory pathway 00:08:19

- E – VIII cranial nerve

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- C – Cochlear division
- O – SON (Superior Olivary Nucleus) → Direction of sound
- L – Lateral leminiscus
- L → Inferior colliculus
- M → Medial geniculate body (Thalamic nucleus)
- A → Auditory cortex (Temporal cortex)

  (BA-41) for perception of hearing

  superior Temporal gyrus / Heschl's gyrus

Attenuation / stapedial reflex 00:12:06

- Loud noise – [Stapedius / Tensor Tympani] – contract → Attenuate sound
- Afferent → VIII Cranial nerve
- Efferent → VII Cranial Nerve
- Nucleus → Superior olivary nucleus

Smell 00:14:10

Odorant Receptor

↓

All odorant receptors are GPCR

↓

Receptors are ⊕ on roof of nasal cavity (Olfactory Epithelium)

↓

Penetrates cribriform plate

↓

#CP → Smell X

↓

Olfactory bulb (Glomerulus)

1.Mitral cells
2.Tufted cells
→ Excitatory → Glutamate

3.Peri glomerular cells
4.Granular cells
→ Inhibitory → GABA

↓

- Anterior olfactory nucleus
- Olfactory tubercle
- Piriform cortex
- Amygdala
- Entorhinal cortex

↓

Relays in

- Thalamus → dorsomedial thalamic nucleus

↓

orbito – frontal cortex

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Orbito – Frontal cortex

Olfactory cortex
↓
Discrimination of smell

Amygdala
↓
Emotions

Entorhinal cortex
↓
Olfactory memory
↓
Degenerated in Alzheimer disease

Taste 00:22:20

1. Sweet → T_1R_2 / T_1R_3
2. Bitter → T_2R
3. Umami → mGlR (MSG)

(1–3: GPCR)

4. Salt
5. Sour

(4–5: ENac channel (Epithelium Na^+ channel))

Taste Pathway 00:24:22

Anterior 2/3rd of tongue
↓
Chorda Tympani VII

Posterior 1/3rd of tongue
↓
IX

Palate / Pharynx
↓
X

Medulla
(Nucleus Tractus solitarius)
(Taste integration station)
↓
Thalamus (VPM)
↓
Taste cortex (Anterior insula)

SPINAL CORD REFLEXES

Reflex

Monosynaptic ↓ Stretch reflex

Bisynaptic ↓ Inverse stretch reflex

Polysynaptic ↓ Withdrawal reflex

Stretch reflex

- Skeletal muscle with intact nerve supply is stretched within physiological limits → Muscle will contract Sensor → Muscle spindle (sense change in length of muscle fibre)

  ↓
  Afferent
  ↓
  Spinal cord
  ↓
  Efferent
  ↓
  Response

Stimulus

- Passive stretch
- All deep tendon reflexes knee jerk / Biceps / Triceps are examples of passive stretch reflux

1 muscle spindle has

↓

3-12 intrafusal fibres

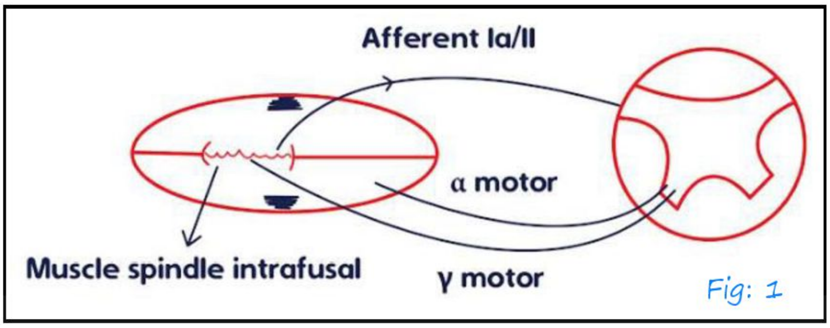

Fig: 1

Sensor: Muscle spindle

Afferent: Ia/II

Efferent: [α-γ coactivation]

- α motor: Contraction of muscle
- γ motor – supply muscle spindle to increase sensitivity of muscle spindle

Intrafusal fibre (Muscle spindle)

- Nuclear bag fibre (2-3)
  - Dynamic nuclear bag fibre ↓ Detect velocity (rate of change of length of muscle fibre)
  - Static nuclear bag fibre
- Nuclear chain fibre (5-9) ↓ Static

Static nuclear bag fibre + Static (nuclear chain fibre) → Sense tonic length of muscle fibre

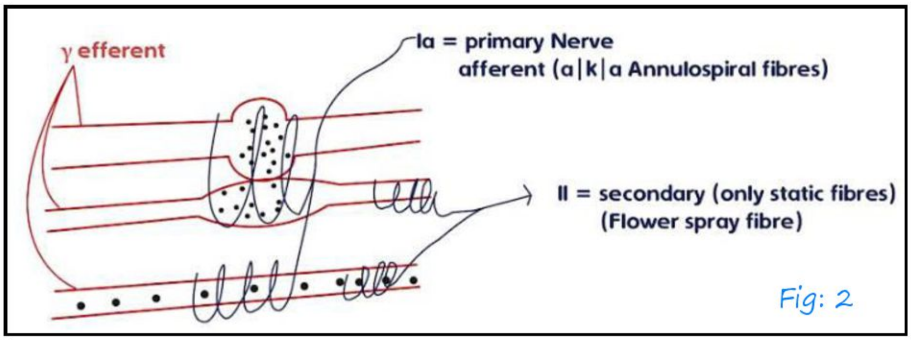
γ efferent
Ia = primary Nerve afferent (a|k|a Annulospiral fibres)
II = secondary (only static fibres) (Flower spray fibre)

Fig: 2

- nuclear bag
  - Ia → Nuclear bag dynamic / nuclear bag static
  - II → Nuclear bag static
- nuclear chain → II
- Ia → Dynamic and static
- II → only static

Efferent:

- γ efferent – Dynamic nuclear bag → Plate endings
  ↓ – Static nuclear bag / Nuclear chain → Trail endings
  It supply peripheral contractile portion of muscle spindle (not central)

Jendrasik Maneuver

- By clenching teeth, increasing γ motor discharge, increase sensitivity in response
- Hypothyroid: delayed reflex (hung – up reflex)
  ↓
  Delayed relaxation phase
- Hyperthyroid: brisk reflexes

Inverse stretch reflex 00:22:35

- It is a type of disynaptic reflex

  Sensor: GTO (Golgi tendon organ)

  Sense: Tension / force / passive stretch – active contraction

  Effect: muscular relaxation [this is protective reaction]

  Inhibition of α motor neuron via interneuron occurs

  ↓

  Renshaw cell

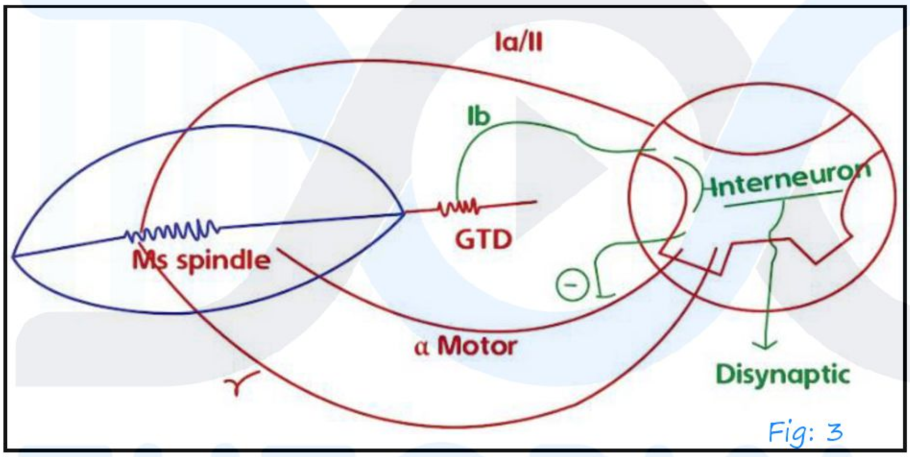

Fig: 3

Stretch reflex	Inverse stretch reflex
sensor: Muscle spindle	Golgi tendon organ tension
Sense: Length	Ib
afferent: Ia / II	Inhibition of α motor
Efferent: α/γ coactivation	↓
↓	Relaxation of muscle
Contraction of muscle	

All deep tendon reflexes are examples of stretch reflex

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Spasticity 00:29:20

- Increase tone in one group of muscles (extensors)
- It is due to increase γ motor discharge

  Example: CLASP – Knife spasticity / lengthening reaction

  ↓

  It is exaggerated form of GTO reflex

  Seen in upper motor neuron disease.

Rigidity 00:31:50

- Increase activity of α motor → Agonist muscle and Antagonist muscle

  Lead pipe rigidity

  Cog wheel rigidity

  Both seen in extrapyramidal disease

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Clonus 00:33:30

- Repetitive muscle contraction in response to stretch due to operation of stretch and inverse stretch
- It is due to increase gamma motor neuron activity

Polysynaptic reflex 00:34:43

- Withdrawal flexor reflex

  Painful stimuli cause flexion on ipsilateral side and extension of contralateral side

Magnet reaction 00:36:25

- Also known as positive supporting reflex
- Pressure over foot pad will cause extension of muscle

5 mass reflex: seen in paraplegic patient

Mild painful stimulus causes – increase in BP, 200mmHg

- Evacuation of bowel x bladder
- Profuse sweating

MOTOR PATHWAY

- Descending Motor Pathway

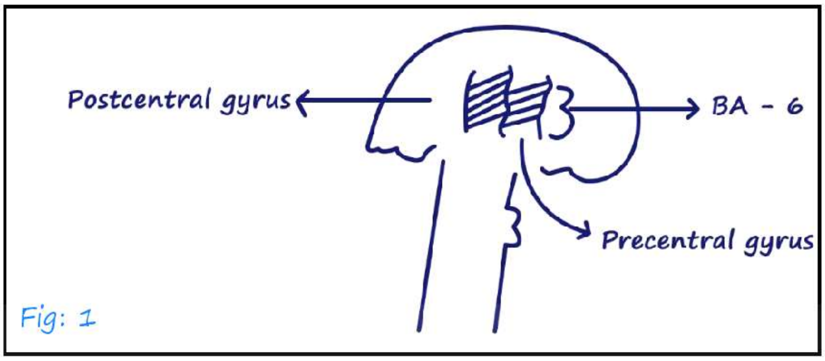


Fig: 1

Precentral gyrus

- B/L cortex & central sulcus

  a/k/a
- 1° motor cortex – Generation of idea

  ↓

  Cortical association area → in frontal lobe

  → Boardman area – 4
- For execution of movement

Post central gyrus

- Behind the central sulcus
- Broadman area 3,1,2
- a/k/a primary somatosensory area
- sensory motor coordination
- before percental gyrus

Premotor cortex → Posture setting

Supplementary motor cortex → Bimanual coordination

- BA-6

Corticospinal tract 00:07:20

- Arise from layer 5 cortex
- 97% pyramidal cells
- 3 % larger giant pyramidal cells → Betz cells

- Coming from
  - 30% – 1° motor cortex
  - 30% – premotor & supplementary motor cortex
  - 40% – somatosensory cortex
    ↓
    (For integration of S-M)

Motor neurons 00:10:30

- UMN
  ↓
  Higher center & controlling LMN
  arise from
  - Cortex
    ↓
    Corticospinal Tract a/k/a pyramidal tract (In Medulla)
  - subcortex
    - Midbrain
    - Pons
    - Medulla

    ↓
    extrapyramidal tract
- LMN
  ↓
  Cranial nerves & Spinal nerves

TUTORIALS LOGIN FOR SUCCESS

- 80% CS fibers cross in Medulla
  ↓
  Lateral corticospinal tract → skilled voluntary activity
- Arise from layer 5
- 3% from Beta cells

- 20% CS fibers does not cross in Medulla

  ↓

  Anterior corticospinal tract → posture

- CS tract regulate LMN supplying skeletal muscle

  - α Motor neurons
  - γ Motor neuron

  } α – γ co-activation

  ↓

  Supply muscle spindle

  - α – contraction of muscle
  - γ –Increase sensitivity of muscle spindle

  ↓

  Maintain muscle tone

Extra pyramidal tract 00:20:20

- reticulospinal tract
- vestibulospinal tract
- tectospinal tract

} Evolution -old

Descent → control – proximal muscles

Medially – paraspinal muscles

Antigravity muscles

Posture control

- rubrospinal tract

  ↓

  - along with pyramidal tract descent laterally
  - Controls distal muscles for voluntary skilled movement
  - Evolution -new

TUTORIALS LOGIN FOR SUCCESS

Reticulospinal tract

Pons	Medulla
Excitatory to antigravity muscle	Inhibitory to antigravity muscle
Both are needed for Limb movement	

Tectospinal tract

- Movement of neck on the body

Decerebrate rigidity 00:28:00

- Cortex & midbrain → corticospinal tract –
  → Rubrospinal tract –
- b/n superior & inferior colliculus
- Reticulospinal tract becomes over active

↓ +

γ– motor neurons → γ – rigidity

↓

Increase rigidity in all 4 limbs

- Hand lies on side of the body – fully extended
- Forearm – pronated
- Clinically seen in uncal herniating
- If cerebellum is also removed
- Extensors rigidity exaggerated

↓

b/c of α motor neuron activation (α–rigidity)

↓

Decerebellate rigidity

Decorticate rigidity 00:35:15

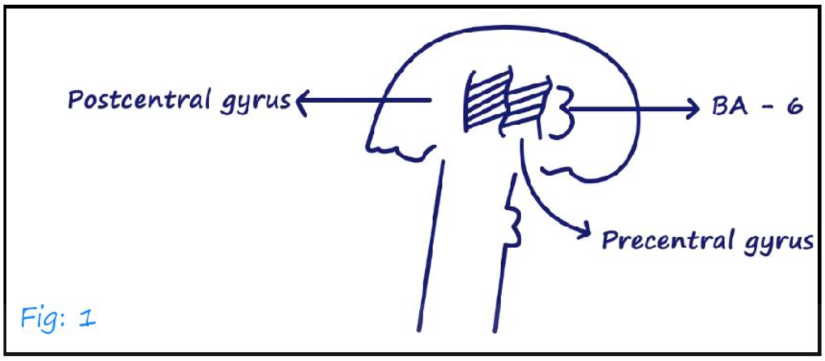
- Only cortex is lost
- CST lost
- Rubrospinal tract intact
- Extension seen only in lower limbs
- Upper limbs are flexed on chest

UMN vs LMN lesion 00:38:30

UMN lesion	LMN lesion
• Muscle reflexes exaggerated	• Muscle reflexes – hypoactive
• Muscle tone → spastic	• Muscle tone – flaccid
• Babinskis-sign → positive	• Babinski sign→ negative, N
• Flexion of great toe	• Flexion of all toes
• Fanning of other toes	• Muscle atrophy prominent
	• Muscle fasciculations +

MOTOR PATHWAY

- Descending Motor Pathway



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    - Medulla

    ↓
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- LMN
  ↓
  Cranial nerves
  &
  Spinal nerves

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CEREBELLUM

[Weight- 10% of cerebral cortex, surface area: 75% of cerebral cortex]

Archicerebellum	Paleocerebellum	Neocerebellum
Floculonodular lobe ↓ Posture & equilibrium (Vestibulo cerebellar pathway)	A/K/A spinocerebellum ↓ Function i. Maintain muscle tone ii. Diadokinesis ↓ Alternated rapid movement	Planning & programing (Coordination of movement)

DOT TUTORIALS
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Vestibulo cerebellum 00:04:00

- Function: Head orientation & rotation

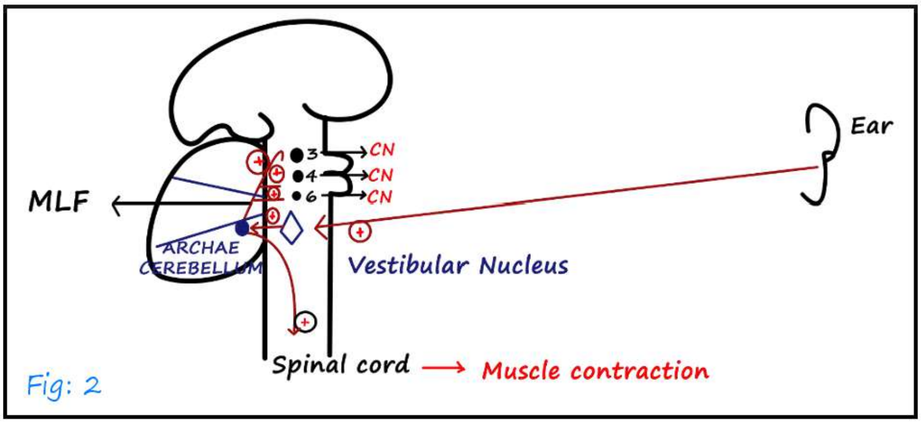

Ear
3
4
6
CN
CN
CN
MLF
ARCHAE CEREBELLUM
Vestibular Nucleus
Spinal cord ⟶ Muscle contraction

Fig: 2

Medial longitudinal fascicular (MLF)

- Important for eye movement
- Function: - saccadic eye movement
  - Vestibulo ocular reflex
  - Optokinetic Reflex
- MLF lesion: Nystagmus: Involuntary jerky eye movements
- Dorsal spinocerebellar → Unconscious proprioception in lower body
- Ventral spine cerebellar → carry one copy of movement & executed via anterior motor neuron
- Cuneo spino cerebellar → they carry unconscious proprioception from head neck, upper thorax
- Olivo cerebellum → converge imp information from Different location
- Tecto cerebellum → it is for coordinating - Auditory impulse
  - Visual impulse
  - Eye hand coordination
- Corticoponto cerebellar Tract → it is the longest tract
  - Concerned with coordination of movement

Cros section of cerebellum 00:16:00

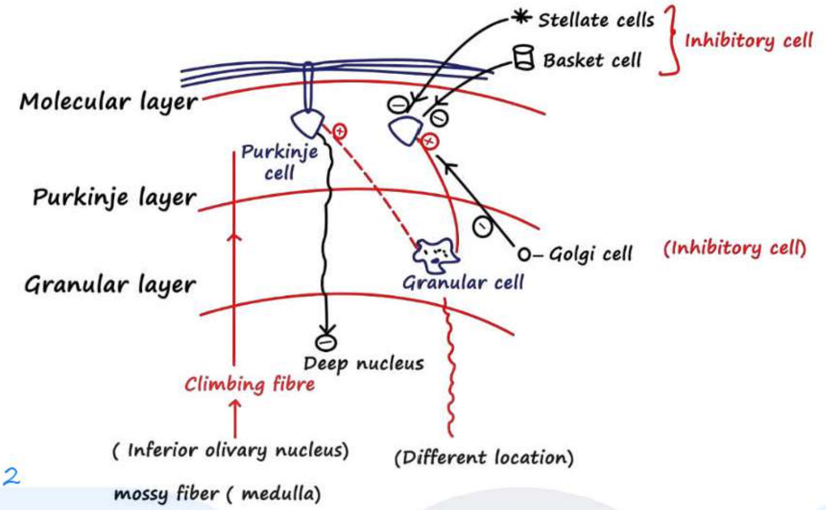

Stellate cells
Basket cell
Inhibitory cell
Molecular layer
Purkinje cell
Purkinje layer
Granular layer
Golgi cell
(Inhibitory cell)
Granular cell
Deep nucleus
Climbing fibre
(Inferior olivary nucleus)
(Different location)
mossy fiber (medulla)

Fig: 2

Mossy fiber should be on right side (refer PDF)

Note:

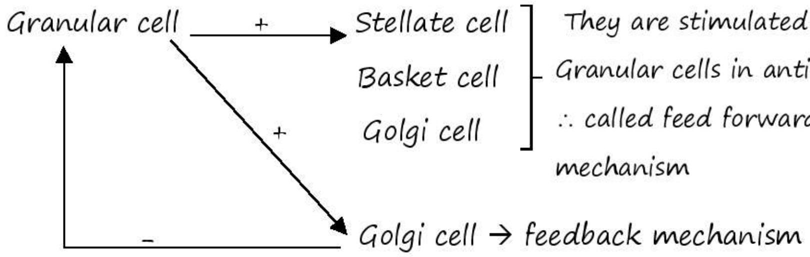
- Granular cells: – only cell which is excitatory (release glutamate)

  – Granular cells form parallel fibers
- Purkinjee cell: – it is only output cell of cerebellum

  – Release GABA ∴ inhibitory

  – Biggest neuron

- Afferents
  - Mossy fiber: stimulate multiple purkinjee cell & cause simple spike
  - Climbing: stimulate single purkinje cell ∴ cause complex spike

- 
Granular cell
+
Stellate cell
Basket cell
Golgi cell
+
–
Golgi cell → feedback mechanism

They are stimulated by Granular cells in anticipation ∴ called feed forward mechanism

Purkinjee cell

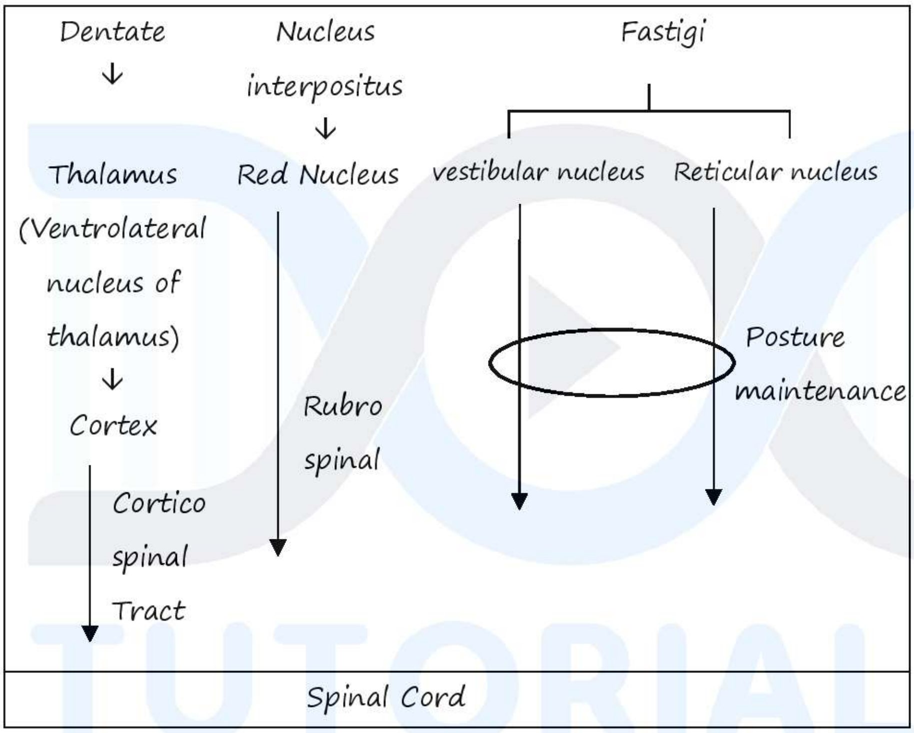
↓ Mnemonic: Don's Eat Girl friend

Deep nuclear

Dentate nuclear

Emboliform nuclear Globosus → Nuclear interpositus

Fastigi


Dentate
Thalamus (Ventrolateral nucleus of thalamus)
Cortex
Cortico spinal Tract
Nucleus interpositus
Red Nucleus
Rubro spinal
Fastigi
vestibular nucleus
Reticular nucleus
Posture maintenance
Spinal Cord

Corticospinal + Rubrospinal] lateral pathway → Regulate Skilled Movement

Disease of cerebellum 00:31:30

- Cerebellar Ataxia (Drunken gait)
- Dysmetria (past pointing) → Finger – Nose test
- Dysdiado kinesia
- Intentional tremor
- Nystagmus

- Pendular knee jerk (due to hypotonicity)
- Hypotonia
- Rebound phenomenon

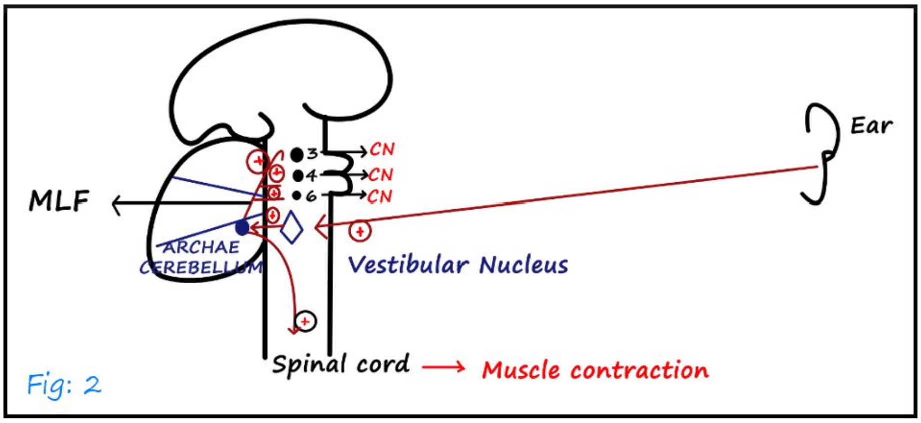
CEREBELLUM

[Weight- 10% of cerebral cortex, surface area: 75% of cerebral cortex]

Archicerebellum	Paleocerebellum	Neocerebellum
Floculonodular lobe ↓ Posture & equilibrium (Vestibulo cerebellar pathway)	A/K/A spinocerebellum ↓ Function i. Maintain muscle tone ii. Diadokinesis ↓ Alternated rapid movement	Planning & programing (Coordination of movement)

Vestibulo cerebellum 00:04:00

- Function: Head orientation & rotation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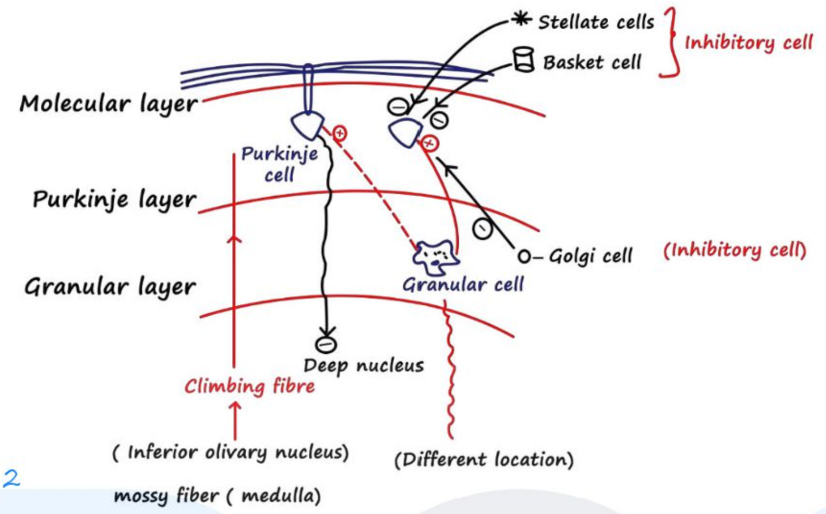
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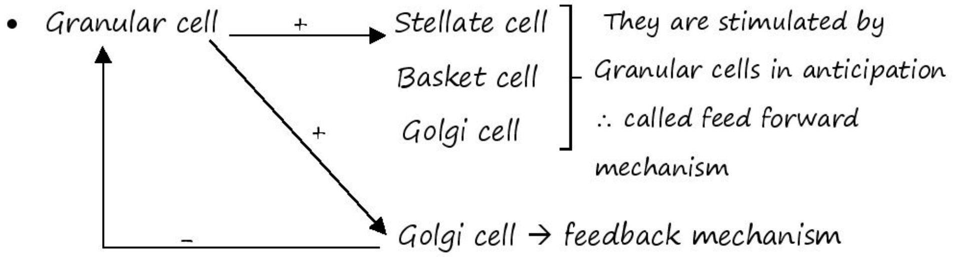
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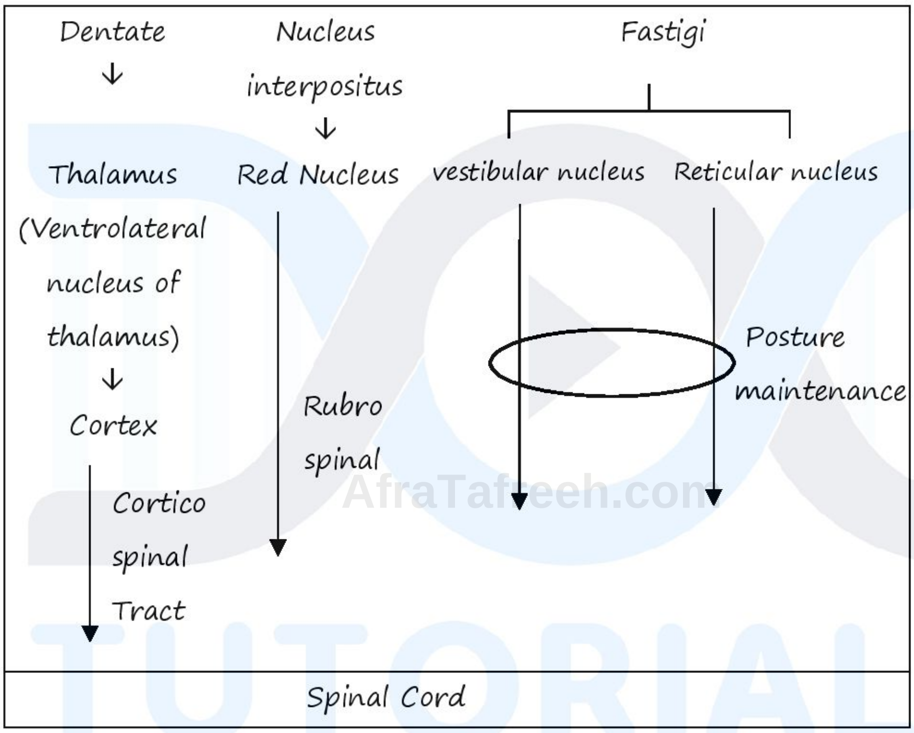
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- Hypotonia
- Rebound phenomenon

BASAL GANGLION

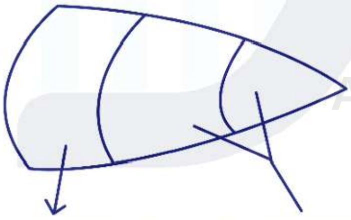
- Basal nucleus
- Inhibitory at rest
- Planning of motor movement

Components 00:01:15

i. Corps striatum- input

- Caudate nucleus
- Putamen

ii. Lentiform nucleus- lens shaped



Putamen + Globus pallidus → Externus

→ Internus- output

iii. Subthalamic nucleus

- Only nucleus which is excitatory
- Release glutamate

iv. Substantia nigra → Pars compacta

→ Pars Reticularis

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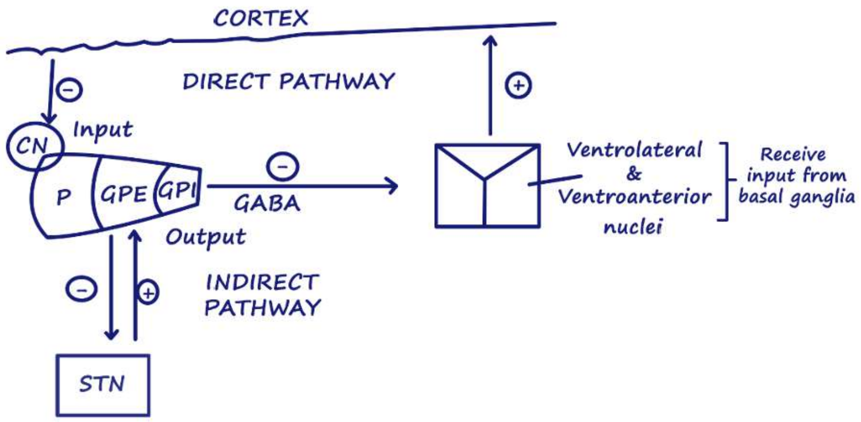
Pathway 00:04:45


CORTEX
DIRECT PATHWAY
⊖
⊕
CN
Input
P
GPE
GPI
⊖
GABA
Output
Ventrolateral
&
Ventroanterior
nuclei
Receive input from basal ganglia
⊖
⊕
INDIRECT PATHWAY
STN

- Direct → excitation of thalamus
- Indirect → inhibition of thalamus

Substantia nigra → Dopaminergic nigrostriatal pathway
↓
D1 & D2 receptors

Pars compacta   pars reticularis

DOC TUTORIALS
LOGIN FOR SUCCESS

Subthalamic nucleus 00:13:15

- Only excitatory
- Controls associated movement like swinging of arm while walking
- Lesions- → BALLISMSUS /HEMI BALLISMUS
  → Flailing movement of extremity

Chorea 00:15:40

→ lesion in corpus striatum

i. Huntington chorea (h gene)

(CAG trinucleotide repeat sequence)

- Lesion in intrastiatal GABA/cholinergic neurons
- Jerky dancing movements

ii. Wilson disease

- Hepatolenticular deposition of copper

iii. Rheumatic fever

- Sydenham chorea

iv. Chorea gravidorum in pregnancy

ATHETOSIS 00:18:55

- Lesion in globus pallidus
- Slow writhing movement
- Dopamine → releases from SN- pars compacta
  ↓
  Striatum

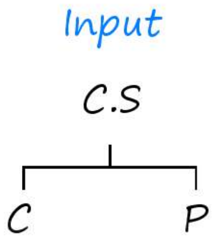
DOT TUTORIALS LOGIN FOR SUCCESS

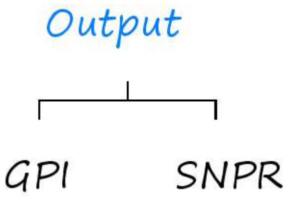
Lesion in SN- pars compacta → Striatum → **Parkinson disease**

- Tremor – resting
- Rigidity –
  - Lead pipe
  - Cogwheel
- Akinesia/bradykinesia
- Pin rolling movement
- Mask face /serpentine look

- SN- pars reticularis $\xrightarrow[\text{GABA}]{-}$ striatum
- STN – receive inhibition from GPE

- STN excites
  - GPE
  - GPI
- SN-PR inhibits VL thalamus




Output
GPI
SNPR

- Target for neurosurgeon for Parkinson disease
  - Ventral lateral nucleus of thalamus

BASAL GANGLION

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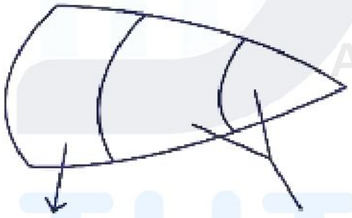

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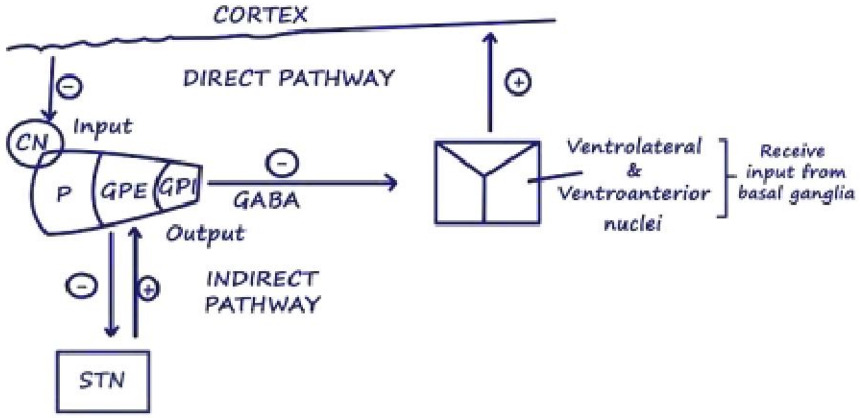
Pathway 00:04:45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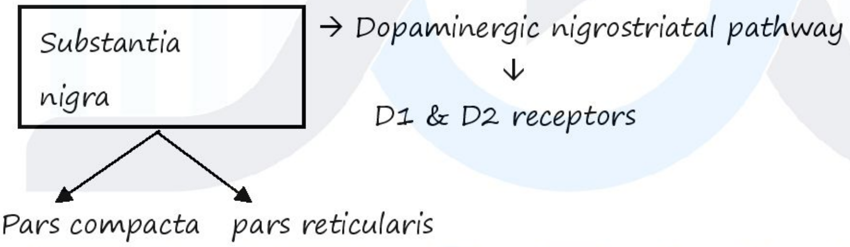
Substantia nigra
→ Dopaminergic nigrostriatal pathway
↓
D1 & D2 receptors
Pars compacta
pars reticularis

DOC TUTORIALS
LOGIN FOR SUCCESS

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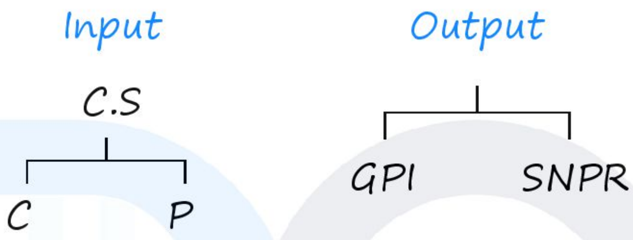

Input
C.S
C
P
Output
GPI
SNPR

- Target for neurosurgeon for Parkinson disease
  - Ventral lateral nucleus of thalamus

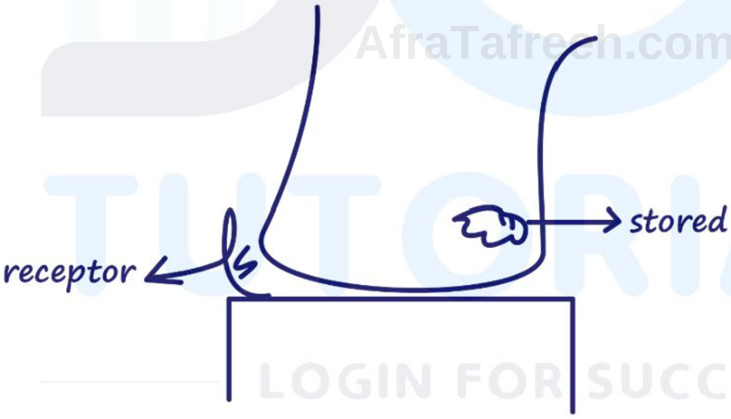
NEUROTRANSMITTER

Classification 00:00:39

- I – Acetylcholine
- II – Biogenic amine
  - Norepinephrine
  - Dopamine
  - Serotonin
  - Histamine
- III – Amino acid
  - Excitatory 75% (Glutamate)
  - Inhibitory → GABA and Glycine
- IV – ATP / NO

Criteria

1. Stored in presynaptic vesicle
2. Receptor on the post synaptic neuron



1. Acetylcholine
   - At NMJ → cause muscle contraction
   - Basal forebrain – nucleus Basalis of meynert
   - Promote REM sleep, learning, memory
   - Sympathetic cholinergic → sweat gland
   - Snare protein → synaptobrevin → Degraded by botulinum toxin

     ↓↓

     Used in form of botox injection

     ↓

     Achalasia cardia, blepharospasm
   - Protein on membrane → Syntaxin
   - Flaccid palsy is caused by botulinum toxin

- Acetylcholine is formed by choline + Acetyl coA

↓

Transported by CHAT (Choline acetyl transferase)

Synthesis and release of acetylcholine needs an important protein called VAT → choline transporter

↓

Blocked by vesamicol

VAT – Vessicle associated transporter → blocked by Hemicholine also

Acetylcholine

- **Ionotropic Nicotinic Receptor**
  - MMJ
  - Neuron
    - CNS
    - ANS
- **Muscarinic**
  - M_1
  - M_2
  - M_3
  - M_4
  - M_5

Gq – M_1 M_3 M_5

Gi – M_2 M_4

CNS – M_1 M_4 M_5

♡ – M_2

Glands smooth m/s → M_3

2. Norepinephrine

- Formed from dopamine

Dopamine ⟶ NE

Dopamine

β hydroxylase

a. Locus coeruleus (Pons)

- Ascends to cortex
- Descend to SC.

↓

- Maintain arousal
- Maintain emotion
- Maintain motivation

  - Pathology causes
  - Anxiety, depression dysthymia
  - Descend downward → Modulate pain stimulating neuron which inhibit pain

b. Lateral tegmentum system

Dopamine

1. Substantia nigra → C. Stratum → Parkinson's disease
2. Ventral tegmetum of mid brain
   - Mid brain
     - Mesolimbic pathway
       - Hippocampus
       - Amygdala
         - Emotions
         - Reward
         - Addicted

         } Nucleus accumbens involved
     - Mesocortical pathway
       - Motivation
       - Planning
       - Attention
3. Tubero infundibulum pathway

   ↓

   Dopamine → Prolactin inhibiting hormone

   → decrease prolactin

   D_1 D_2 D_3 D_4 D_5 = GPCR

Serotonin 00:21:20

- 5 Hydroxytryptamine ($5HT_1$ to $5HT_7$)
- All are GPCR except 5 HT_3 → Ionotropic
- Synthesized from tryptophan with help tryptophan hydroxylase
- $5HT_{2A}$ – important for platelet aggregation& smooth muscle contraction

  $5HT_{2C}$ → GIT / Satiety / hunger is decreased

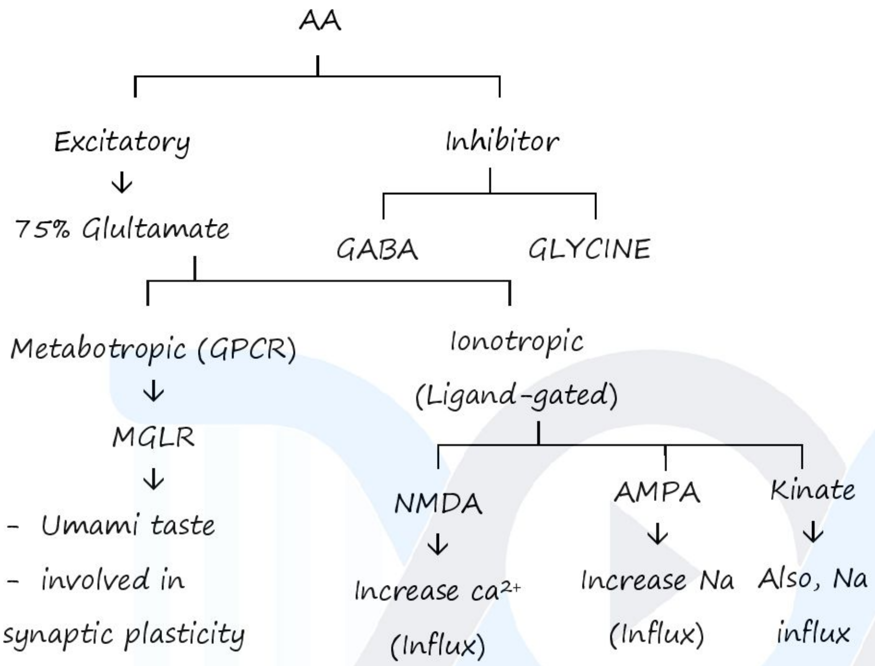
  $5HT_3$ → concerned with vomiting

  $5HT_4$ → peristalsis

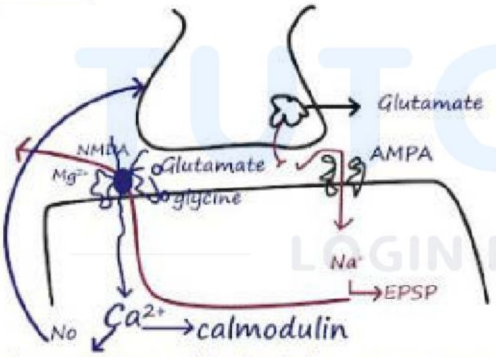
  $5HT_{6/7}$ → limbic cortex
- All serotonins are inhibitory neuro transmitters

Histamine 00:25:44

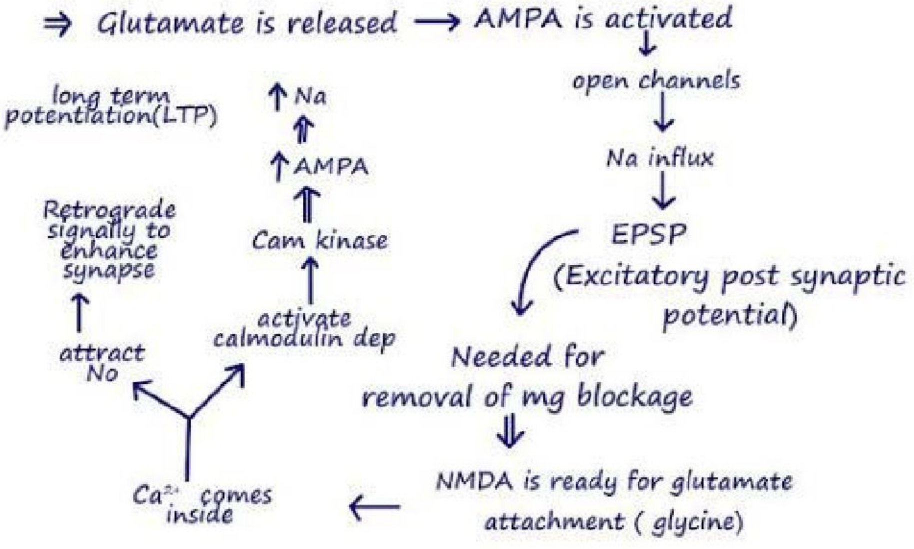
- Histidine derivative
- Released from posterior hypothalamus (Tubero mamillary nucleus)
- H_2 → gastric secretion – increase Hcl
- H_4 → immune system – H_1 – H_4


AA
Excitatory
75% Glultamate
Inhibitor
GABA
GLYCINE
Metabotropic (GPCR)
MGLR
- Umami taste
- involved in synaptic plasticity
Ionotropic (Ligand-gated)
NMDA
Increase ca^{2+} (Influx)
AMPA
Increase Na (Influx)
Kinate
Also, Na influx

NMDA


Glutamate
NMDA
Mg^{2+}
Glutamate
glycine
AMPA
Na^+
EPSP
No
Ca^{2+} → calmodulin

⇒ NMDA - blocked by magnesium


⇒ Glutamate is released → AMPA is activated
open channels
Na influx
EPSP
(Excitatory post synaptic potential)
Needed for removal of mg blockage
NMDA is ready for glutamate attachment (glycine)
Ca^{2+} comes inside
activate calmodulin dep
Cam kinase
↑ AMPA
↑ Na
long term potentiation(LTP)
attract No
Retrograde signally to enhance synapse

- Concentrated maximum in hippocampus

  ↓↓

  Short term memory → long term memory
- Blockade of NMDA can prevent long term potentiation (LTP)
- Activation of NMDA by
  - Removal of magnesium. blockade by EPSP – AMPA
  - Glutamate
  - Glycine
- Blockage of NMDA by
  - Felbamate
  - Phencyclidine
  - Ketamine → dissociative anesthesia → disconnects higher brain / lower brain
- Glutamate induced cell death

  ↓↓

  Huge calcium influx

  Glutamate antagonist needed (NMDA Antagonist)
  - Memantine → Alzheimer disease
  - Riluzole → Amylotropic lateral sclerosis

GABA

- Both metabotropic and Ionotropic
- 3 types
  - A
  - B → Metabotropic → K efflux
  - C
- A + C – Ionotropic receptor – cl influx
- GABA – inhibitory
- GABA C – exclusively found in retina
- GABA causes hyperpolarization → sedation
- GABA – A Agonists
  - Benzodiazepine
  - Barbiturates
- GABA – B Agonists → Baclofen → used for severe muscle spasticity

Glycine

- Inhibitory
- Excititatory → helps to activate NMDA receptor → glutamate
- Renshaw cell inhibit motor neuron
- Spinal poison – inhibit RC → Spastic paralysis

- Antagonist of glycine – Strychnine → antagonizes glycine

tetanospasmin (c. tetani)
↓
Inhibits RC
↓
Cannot release glycine
↓↓
Tetanus / spastic paralysis

HYPOTHALAMUS & LIMBIC SYSTEM

Food Intake

Satiety	Hunger
↓	↓
Ventromedial nucleus	Cateral nucleus
Lesion: increase food intake / obese	Lesion: increase food intake / thin
Stimulated: decrease hunger / thin	Stimulated: decrease hunger / obese

Activate Nucleus

	Anorexins	Orexins
They Regulate satiety	i. CART Cocaine amphetamine regulated transcription ii. α MSH	Increase Hunger i.Neuropeptide-Y ii. AGRP "Agouti gene related peptide "

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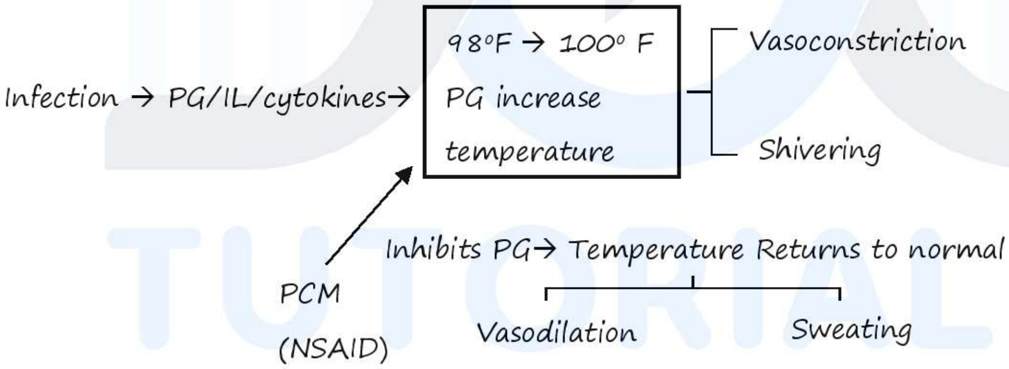
Body Temperature

AC
↓
Anterior Hypothalamic Nucleus
↓
Respond to heat
↓
Cause sweating/Vasodilation thirst
Lession: Fever

Heater
Posterior Hypothalamic Nucleus
Respond to cold
↓
Shivering/vasoconstriction/ Increase frequency of urine.
Lession: Hypothermia



Infection → PG/IL/cytokines→ 98°F → 100° F PG increase temperature → Vasoconstriction, Shivering

PCM (NSAID) → Inhibits PG→ Temperature Returns to normal → Vasodilation, Sweating

DOC TUTORIALS LOGIN FOR SUCCESS

SLEEP

Wakefulness
i.Lateral hypothalamic nucleus
↓
Orexins
Loss of orexins → Narcolepsy
ii. Posterior Hypothalamic Nucleus
↓
Histamine
∴ Antihistamines cause sleepiness

Sleep
i.Preoptic nucleus
↓
Ventrolateral preoptic nucleus

Memory

↓

- Mamillary body → alcohol cause degeneration

∴ ↓

i. Confusion
Confabulation present ← ii. Memory loss — Wernicke-Korsakoff psychosis
iii. Ataxia

Treatment: thiamine injection

Endocrine Regulation 00:16:30

Releasing Hormone
↓
GnRH/GHRH/CRH

Inhibitory Hormones
↓
- Growth Hormone inhibiting hormone
- Prolactin inhibiting hormone
↓
Dopamine

Supraoptic nucleus
ADH>>> oxytocin
a.k.a vasopressin
↓
Released based on osmoreceptors
↓
Present in Anterior hypothalamus
(Pre optic nucleus)

Para ventricular Nucleus
↓
Oxytocin >> ADH

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AllaTaleem.com

Dorsomedial nucleus

↓

- Stimulation leads to aggression /Anger

↓

Called SHAM RAGE – in Animals hissing seen

∴ Cortex control sham rage ↳ eliminated by Ablation of
(Decortication) Hypothalamus

Supra chiasmatic nucleus

↓

Control circadian Rhythm

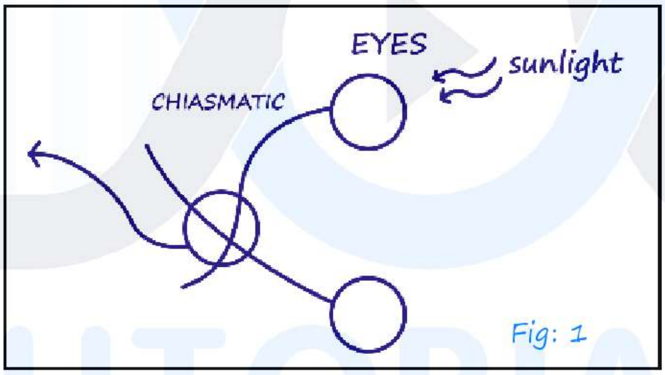

Fig: 1

Sunlight → external clue, even if external clue is abolished, circadian rhythm is maintained ∴ internal clues are also present but biological clock will be little prolonged (24→ 25 hr)

Note:

- **ACTH** → -Maximum in Morning
  -Minimum in Night

↓

Cortisol

Reward center

↓

Medial fore brain Bundle

↓

Nucleus accumbens (Dopamine involved)

Sexual Behavior

↓

Preoptic nucleus Regulate sexual Behavior

↓

(Secrete GnRH)

Limbic system 00:27:35

- It is Rim of cortical tissue old in evaluation
- It is concerned with smell

↓

∴ called Rhinencephalon

i. Cingulate gyrus:

Influence – ANS ∴ BP/HR

- Cognition
- Attention
- Emotion

ii. Para Hippocampal gyrus: spatial memory

iii. Hippocampus: It has NMDA receptor

↓

Convert short term to long term memory

iv. Amygdala: window of limbic cortex

Bilateral destruction of Temporal lobe:

↓

Amygdala Destruction

↓

kluver Bucy syndrome

Increase Libido
Hyperorality
Placidity
Loss of fear

Dysfunction of Amygdala

- Anxiety
- Fear
- Emotion
- Aggression

v. Hypothalamus

vi. Mamillary body: Memory, lip movement

vii. Nucleus accumbens: reward center, Addiction

Papez circuit 00:35:10

- Concentrates with

↓

- Memory
- Emotion
- Learning

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LIMEMONIC _ HMT CPE

- Hippocampus —Fornix→ Mammillary body → anterior thalamic nucleus

"Performant pathway: ↑

internal capsule ↓

EnteroRhinal cortex ← para hippocampal gyrus ←cingulate gyrus

HYPOTHALAMUS & LIMBIC SYSTEM

Food Intake

Satiety
↓
Ventromedial nucleus
Lesion: increase food intake / obese
Stimulated: decrease hunger / thin

Hunger
↓
Cateral nucleus
Lesion: increase food intake / thin
Stimulated: decrease hunger / obese

Activate Nucleus

Anorexins

They Regulate satiety
- i. CART
  Cocaine amphetamine regulated transcription
- ii. α MSH

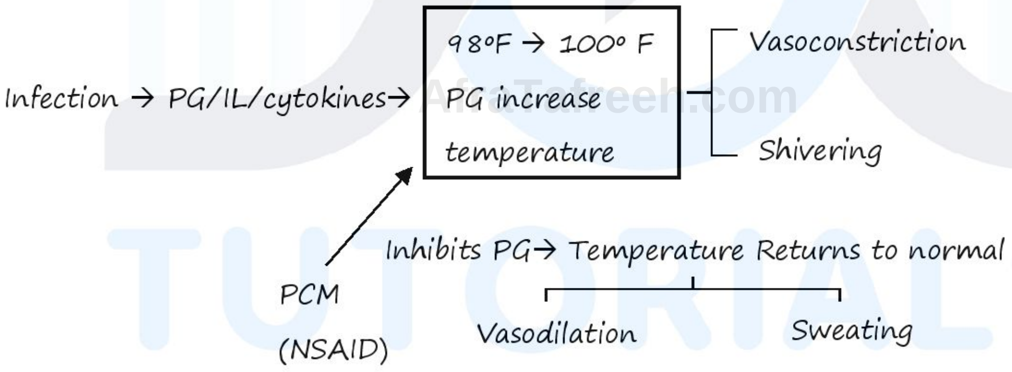
Orexins

Increase Hunger
- i.Neuropeptide-Y
- ii. AGRP
  "Agouti gene related peptide "

Body Temperature

AC
↓
Anterior Hypothalamic Nucleus
↓
Respond to heat
↓
Cause sweating/Vasodilation thirst
Lession: Fever

Heater
Posterior Hypothalamic Nucleus
Respond to cold
↓
Shivering/vasoconstriction/ Increase frequency of urine.
Lession: Hypothermia


Infection → PG/IL/cytokines→
98°F → 100° F
PG increase temperature
Vasoconstriction
Shivering
PCM (NSAID)
Inhibits PG→ Temperature Returns to normal
Vasodilation
Sweating

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SLEEP

Wakefulness
i.Lateral hypothalamic nucleus
↓
Orexins
Loss of orexins → Narcolepsy
ii. Posterior Hypothalamic Nucleus
↓
Histamine
∴ Antihistamines cause sleepiness

Sleep
i.Preoptic nucleus
↓
Ventrolateral preoptic nucleus

Memory

↓

- Mamillary body → alcohol cause degeneration

∴ ↓

i. Confusion
ii. Memory loss → Confabulation present
iii. Ataxia

(i–iii) Wernicke-Korsakoff psychosis

Treatment: thiamine injection

Endocrine Regulation 00:16:30

Releasing Hormone
↓
GnRH/GHRH/CRH

Inhibitory Hormones
↓
- Growth Hormone inhibiting hormone
- Prolactin inhibiting hormone
↓
Dopamine

Supraoptic nucleus
ADH>>> oxytocin
a.k.a vasopressin
↓
Released based on osmoreceptors
↓
Present in Anterior hypothalamus
(Pre optic nucleus)

Para ventricular Nucleus
↓
Oxytocin >> ADH

Dorsomedial nucleus

↓

- Stimulation leads to aggression /Anger

↓

Called SHAM RAGE – in Animals hissing seen
∴ Cortex control sham rage ↳ eliminated by Ablation of
(Decortication) Hypothalamus

Supra chiasmatic nucleus

↓

Control circadian Rhythm

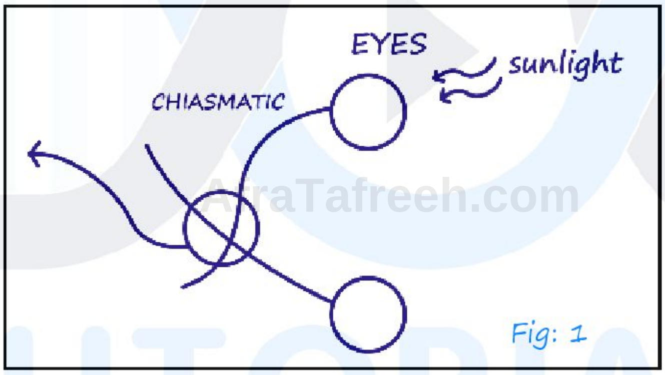

Fig: 1

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Sunlight → external clue, even if external clue is abolished, circadian rhythm is maintained ∴ internal clues are also present but biological clock will be little prolonged (24→ 25 hr)

Note:

- **ACTH** → -Maximum in Morning
  ↓ -Minimum in Night
  Cortisol

Reward center

↓

Medial fore brain Bundle

↓

Nucleus accumbens (Dopamine involved)

Sexual Behavior

↓

Preoptic nucleus Regulate sexual Behavior

↓

(Secrete GnRH)

Limbic system 00:27:35

- It is Rim of cortical tissue old in evaluation
- It is concerned with smell

↓

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- Emotion

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Papez circuit 00:35:10

- Concentrates with

↓

- Memory
- Emotion
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LIMEMONIC _ HMT CPE

- Hippocampus $\xrightarrow{\text{Fornix}}$ Mammillary body → anterior thalamic nucleus

"Performant pathway:

internal capsule

EnteroRhinal cortex ← para hippocampal gyrus ←cingulate gyrus

EEG & SLEEP

EEG → Electroencephalogram

- Discovered by Hans Berger.
- Father of EEG
- Represents overall activity of brain
- Summated potential

α – Wave: (Alpha) 00:01:10

- Eyes close/ relaxed/ Inattentive
- Frequency → 8 –13 Hz
- Increase in low frequency α wave is seen in:
  - Hypothermia
  - Hypoglycemia

- α – waves are prominent in parieto-occipital region.
  α – block is seen when eyes opened

β – Wave: (Beta) 00:04:08

- Frequency → 13–30 Hz
- Amplitude is less,Frequency is high
- Eyes open/attentive
- These are prominent in parieto-frontal region

Theta wave 00:05:30

- a.k.a memory waves

- Frequency → 4-7 Hz
- More common in children
- NREM sleep stage I
- Seen in Hippocampus when short term memory is converted into long term memory.

Delta waves: (δ) 00:06:55

- Frequency → 4 Hz
- More common either in deep sleep – NREM stage III, IV
- Deep coma
- Deeper anaesthesia
- In organic brain disease
- Very slow frequency wave

Gamma waves (y) 00:08:21

- Max frequency during – Focused attention
- Frequency → > 60 Hz
- According to frequency

  Mnemonic – y BAT dance (decreasing order of frequency)

y	β	α	Theta	δ
↓	↓	↓	↓	↓
60 Hz	13-30	8-13	4-7	< 4

Sleep 00:10:02

- Normally we have 4-5 cycles (each of 90-110 min)

NREM	REM
• 60-70 min	• 15 min
• Non rapid eye movement	• Rapid eye movement

- Sleep starts with NREM then REM, then NREM
- As sleep continue NREM decrease, REM increases
- During Narcolepsy → sleep starts directly from REM.

NREM Sleep 00:12:50

- Non rapid eye movement sleep
- Deep sleep/ Actual sleep/ Quiet sleep/ Orthodox
- There are 4 stages of NREM

NREM – I → α wave → Theta wave

NREM – II →

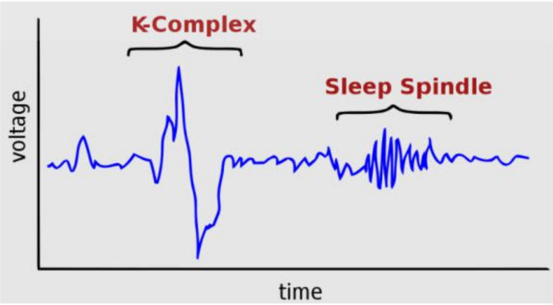

Fig: 1

Stage I, II called as light sleep

NREM – III → δ wave appears for 1st time

NREM – IV → >50% gamma waves are seen

- NREM II has longest duration

Changes in NREM

- Decrease body movement
- Decrease temperature
- Decrease BP
- Decrease heart rate
- Decrease respiratory rate → slow & deep
- RR decreases in both REM & NREM

REM Sleep 00:17:31

- Rapid eye movement
- Brain is active; body is like paralysed, so we see α, β waves
- Muscle atonia – except extra ocular muscles and diaphragm
- 1st muscle to get atonia → neck muscle (cervical)
- BP increases
- HR increases
- In males there can be penile erection and sexual arousal in both males, females.

REM

- A.k.a – paradoxical/ Active/ Superficial

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Dreams 00:21:18

- These are seen in both REM & NREM but are different

REM Dreams	NREM Dreams
↓	↓
Very long	Short
Visual	Less emotional
Emotional	Conceptual
Not connected to reality (fictional)	Related to reality

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Wakefulness is promoted by:

- RAS (Reticular Activating System) → Release NE
- Lateral hypothalamus → Release orexin; Hypocretin
  Loss of orexin causes – Narcolepsy
- Posterior hypothalamus → release histamine
  Antihistamines – cause drowsy
- Raphe nucleus – serotonin.

Sleep promoting areas in brain:

- Hypothalamus → ventro-lateral pre-optic nucleus
- Pineal gland → release melatonin
- Jet lag is treated by melatonin agonist – Ramelteon
- Pineal gland along with supra chiasmatic nucleus maintain biological clock.
  Pons/midbrain – REM sleep – because of Ach.
  Ach → induce REM sleep

The following are seen in NREM

- Bruxism – teeth grinding – seen in NREM – II
- Sleep walking/ sleep talking – NREM III, IV

  ↓

  Somnambulims
- Enuresis

  - Bed wetting – normal in children

  - Alarm clock method is used as management

  - Drug – Desmopressin – Has high relapse rate.
- Pavornocturnus – night terror – (forget what happened)

In REM –

- Night mare – (Remember the whole)
- Narcolepsy

LEARNING AND MEMORY

Learning 00:00:25

Acquisition of new information / skill

Cerebral hemisphere

Right

- Non dominant

↓

- Representational

↓

- Intuition based thinking
  - Art / Music / Dance
  - Spatial memory

Lesion

- Hemispatial neglect
- Astereognosis

Left

- Dominant hemisphere also known as categorical hemisphere
- Dominant in 96% right-handed
- 70% left-handed
- Logic based thinking
  - Language
  - Speech
  - Memory
  - Maths

Lesion

- Aphasia

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Memory 00:06:10

storage

1.Declarative memory / Explicit memory

- Place / fact / event

Semantic	**Episodic**
• Lateral and anterior temporal cortex	• Medial temporal lobe and hippocampus
• Prefrontal cortex	

2.Non declarative / Implicit memory

- Subconscious

i. PROCEDURAL

- Learnt skill
- Basal ganglion (Corpus striatum)

ii. PRIMING

- Neo cortex

iii. CONDITIONING (associative learning)

- Amygdala
- Cerebellum

a)Classical

Dog + Food = salivate (innate reflex)

Dog + food + Ring bell = salivate (Innate reflex)

Dog + Ring bell = salivate (Classical conditioning)

↓

Pavlov

b) Operant

- Punishment based learning

iv. Non – Associative

sensitization

- Increase response to continuous stimuli
- [Post tetanic potentiation]

long term potentiation

↓↓

Hippocampus

- STM ↓→ Long term memory

Hippocampus

- CA1 (Memory neuron)

Direct Indirect

Habituation

- Decrease response to continuous stimuli

↓

Long term depression

↓

synaptic weakening

Direct Pathway

Enterorhinal cortex / Limbic cortex

↓ (activate)

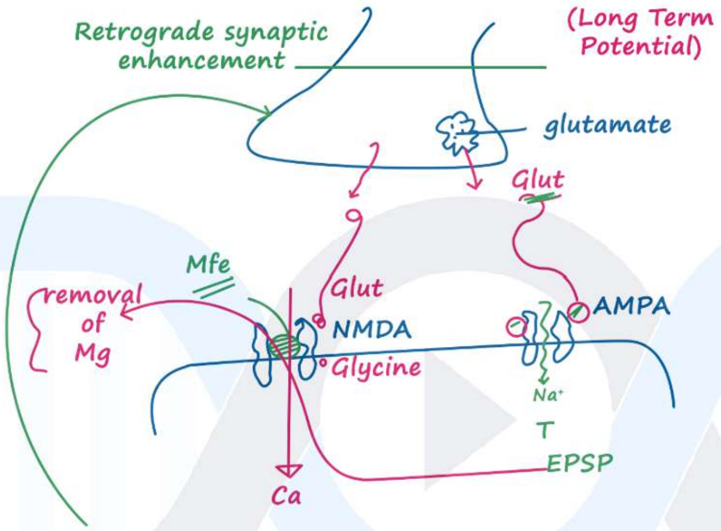
CA-1 Neuron

Indirect Pathway

- ERC $\xrightarrow{\oplus}$ Dentate part of Hippocampus $\xrightarrow{\oplus}$ CA3 $\xrightarrow{\oplus}$ CA-1

- Shouffer collateral

  Long term potentiation ~ Hippocampus


Retrograde synaptic enhancement
(Long Term Potential)
glutamate
Glut
Mfe
removal of Mg
Glut
NMDA
Glycine
AMPA
Na+
T
EPSP
Ca

Mfe- Mg ion

- Glutamate activates AMPA first b/c NMDA always blocked by Mg ions
- Allows influx of Na$^+$ ions resulting in attachment of glutamate and glycine to NMDA → Influx of Ca^{2+} ions → Ca^{2+} → CAM kinase → AMPA → EPSP → Mg removal

Ca^{2+} → NO → Retrograde synaptic enhancement

↓

Long term potentiation

CA – 1 Neuron – also known as SOMMER sector

↓

Lesion

- Intact procedural memory / skills
- No new memory

↓

Anterograde amnesia

Speech 00:28:00

1. Broca's area → Motor area / word formation

   Inferior frontal cortex

   ⊖ → Broca's aphasia – fluency lost – BA-44

   - Non fluent aphasia
   - Understanding / comprehension – intact
   - Follows command
   - Repetition lost

2. Wernick area (Sensory area) BA – 22
   - Comprehension / understanding
   - Superior temporal gyrus

     ⊖ → Wenicke's aphasia / sensory aphasia

     - Fluent aphasia
     - Neologism
     - Comprehension lost
     - Repetition lost

3. Conduction aphasia

- Arcuate fiber lesion
- Fluency intact
- Comprehension intact
- Repetition lost

4.Anomic aphasia BA – 39

- Problem in the written language
- Lesion of angular gyrus

Alzheimer's disease 00:38:55

- Most common age-related disease of memory loss
- Neurodegenerative disorder
- Mutations in
  1.Amyloid precursor protein
  2.Presenilin – 1 / presenilin – 2
  3.Down syndrome
- Senile plaques accumulated

↓

I/t intracellular neurofibrillary tangles

↓

Degenerate cholinergic neurons

Cortex Hippocampus

Management

- Acetylcholinesterase inhibitors
- Donepezil / galantamine
- Rivastigmine / Tacril

Memantine (NMDA Antagonist)

- Prevent glutamate toxicity

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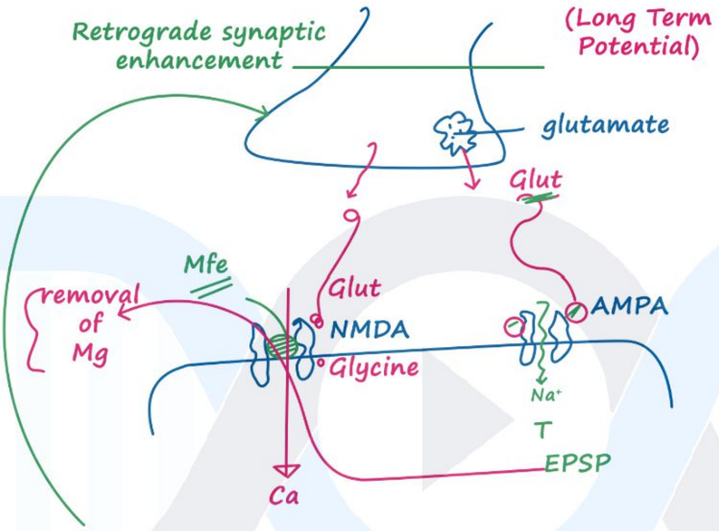
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↓

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- Rivastigmine / Tacril

Memantine (NMDA Antagonist)

- Prevent glutamate toxicity

CSF

- Lubrication
- Volume – 150ml
- Rate of production – 550ml/day
- CSF pressure – 70-80mm of water

Produced by choroid plexus

Absorbed by arachnoid villi (Regulation of CSF pressure exclusively by absorption)

- Chloride / Mg / PCo_2 → more in CSF than plasma
- Osmolarity and HCO_3^- →same in CSF and plasma

  Less in CSF than plasma
- Glucose = 2/3 of blood concentration
- Proteins – (15-45mg/dl)
- K^+ and Ca^{2+}
- Cerebral blood flow – 750ml/min   liver

  55ml/100fm/min   1500ml/min
- More in grey matter > white matter

  O_2 consumption ~ 20% Total O_2 consumption

  ~ 46 ml/min
- More susceptible to hypoxia (Hippocampus)

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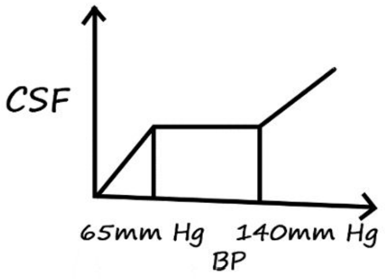


→ Auto regulation

-CSF pressure does not change from 65mmHg to 140mmHg of blood pressure

- Most sensitive stimulus – CO_2

  Increase Co_2 – increase CBF

  1° decrease in body temperature – 7% decrease in CBF

  Hypothermia – used for surgery brain to minimize blood flow

Blood – Brain barrier

- Tight junctions between endothelial cells
- Astrocytes regulates permeability of BBB
- Substances that cross BBB
  - Lipid soluble substances
  - O_2
  - CO_2
  - Nitrogen via
  - Glucose – GLUT – 1
  - Water – Aquaporin
- Cannot cross BBB
  - Water soluble peptides
  - Protons (H^+)
  - Dopamine
- Circumvallate organs – away from BBB

M – Median eminence of hypothalamus

S – Subfornical area

O – Organum vasculosum of lamina terminalis

A – Area postrema

P – Posterior pituitary

If CSF increase

Blood decrease

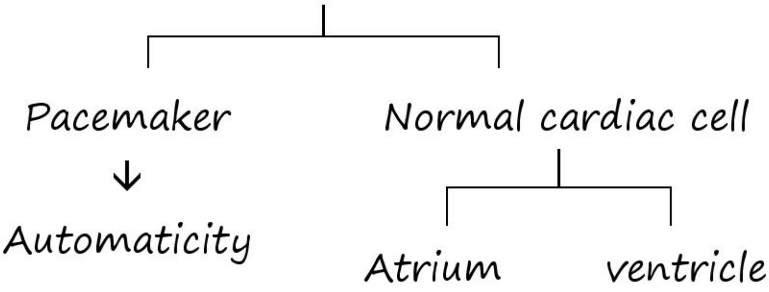
Brain parenchyma decrease

↓↓

Monro kellie doctrine.

ELECTRICAL ACTIVITY OF HEART

Electrical activity of heart output


Pacemaker
Automaticity
Normal cardiac cell
Atrium
ventricle

- you have a RMP and a threshold

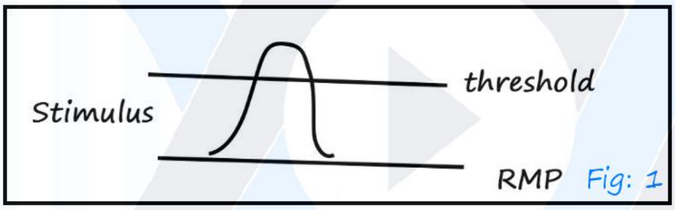

Stimulus
threshold
RMP

Fig: 1

- Whenever you give stimulus, RMP reaches threshold and there would be depolarization and repolarization
- But, in SA node, AV node, pacemaker, you dont have stimulus

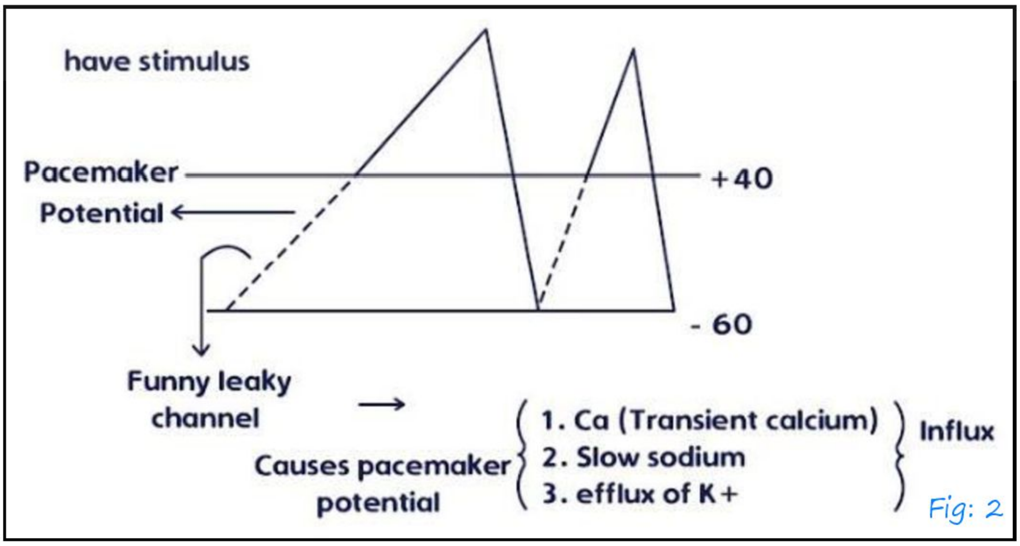

have stimulus
Pacemaker
Potential
+40
- 60
Funny leaky channel
Causes pacemaker potential
1. Ca (Transient calcium)
2. Slow sodium
3. efflux of K+
Influx

Fig: 2

- Your heart have funny leaky channels

  ↓↓

  They keep on leaking like that

  ↓↓

  As they reach the threshold → it causes depolarization → repolarization

  ↓↓

  Same repeats
- Pacemaker potential is also called as pre potential (diastolic potential)
- Funny leaky channel also known as HCN channel (Hyperpolarization induced cyclic AMP dependent nucleotide channel)

  ↓↓

  Voltage gated + ligand gated channel

  Both
- Cause of depolarization / upstroke → influx of calcium (long lasting)
- Cause of repolarization → outflux of K

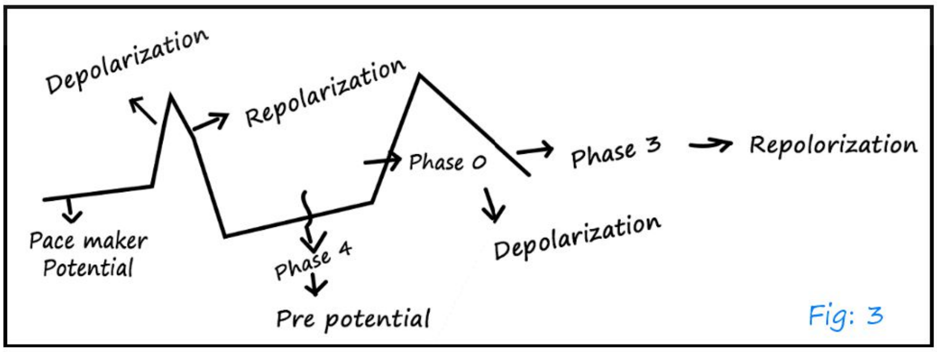

Depolarization
Repolarization
Phase 0
Phase 3
Repolorization
Pace maker Potential
Phase 4
Pre potential
Depolarization

Fig: 3

- If blocker = Ivabradine

  ↓↓

  - Used to decrease HR
  - Side effects → decreases visual activity
- Normal heart rate: - 60-100

  <60 – Bradycardia

  >100 – Tachycardia

  Positive → HR increased

  Negative → HR decreased

  ] Chronotropy
- In the heart, you have β_1 adrenergic receptor → sympathetic

  M_2 receptor → parasympathetic

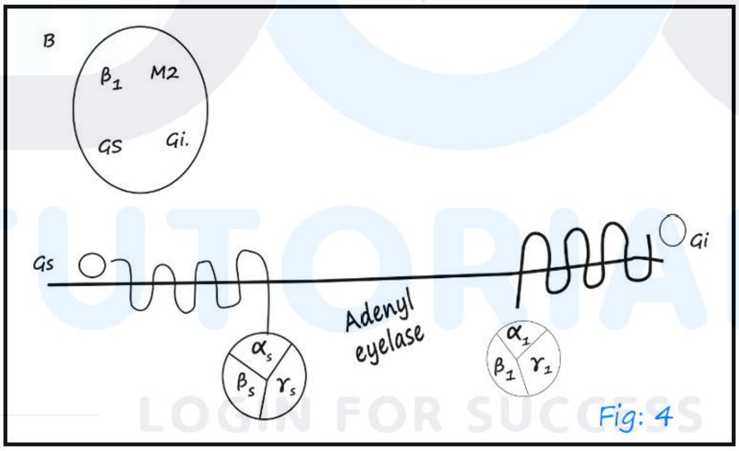


Fig: 4

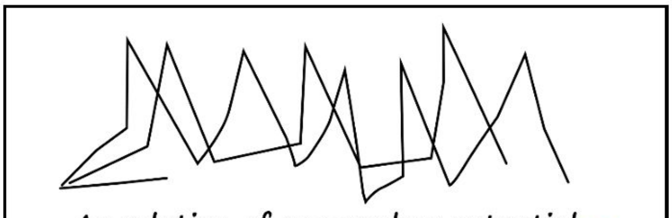
- Adrenaline will stimulate β_1 receptor

  ↓↓

  Increase CAMP → positive chronotropy increase HR
- Acetylcholine will activate M_2 receptor

  ↓↓

  Decrease CAMP → negative chronotropy decrease chronotrophy decrease HR


Angulation of pacemaker potential Fig: 5

- If you are under sympathetic stimulation

  ↓↓

  Slope of pre – potential increase
- If you are under parasympathetic

  Stimulation → slope of pre potential decrease

  ACTION POTENTIALS

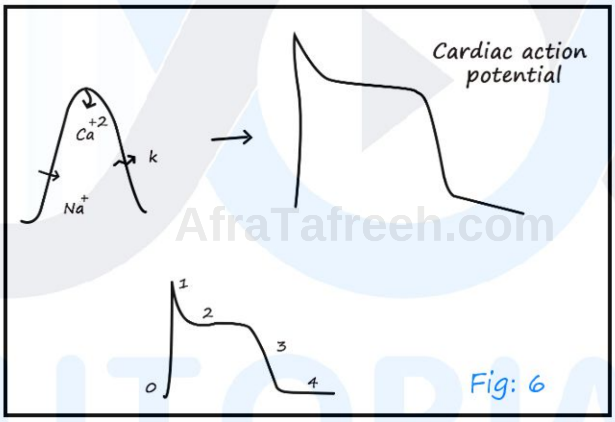


Fig: 6

- Phase 0 – Depolarization – Na Influx
- Phase 1 – Early repolarization – K Efflux
- Phase 2 – Plateau – K Efflux / Ca influx
- Phase 3 / late repolarization – k efflux
- Phase 4 / RMP – Na^+ – k^+ Pump

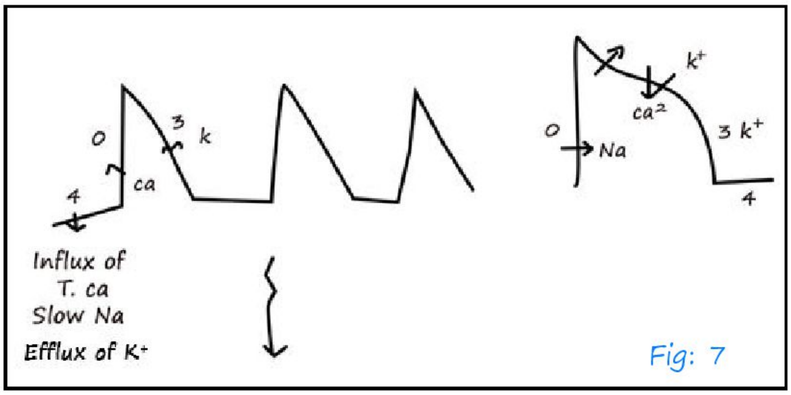


Fig: 7

- SA mode → pacemaker as it generates impulse around 60-100
- AV node – 40-60
- Bundle of his – 40-20
- SA node is always under influence of vagal tone → parasympathetic supply to heart
- If vagus nerve is CUT → HR will increase
- Atropine → parasympathetic blocker

↓↓

Increase HR

	SA node	AV node
Sympathetic	Right stellate ganglion	Left stellate ganglion
Parasympathetic	Right vagus nerve	Left vagus nerve

Stoke adam syndrome

- Also called as overdrive suppression
- If SA node is not working properly, AV node will become pacemaker

↓

HR <30 → dizziness

<10-20 → syncope

↓↓

Stoke adam syndrome

Dromotropy

- Regarding conducting system of heart

  ↓↓

  Modified cardiac muscle
- From SA node → AV node, there are 3 bundles
  - Anterior bundle of Bachman
  - Middle is of Wenckebach
  - Posterior fiber of thorel
- From AV node, they go to bundle of his and give RBB and LBB

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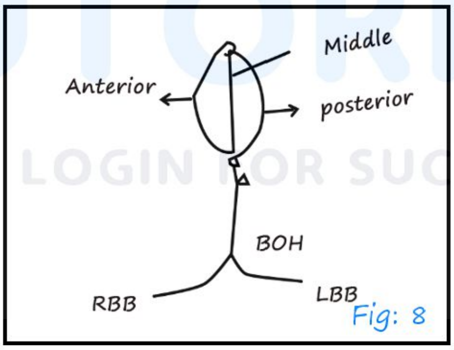

Fig: 8

- Time interval from SA node to AV node → 30ms
- AV nodal delay is 130ms → 0.13 seconds
- From AV node → bundle of his (BOH) → 40ms
- From SA node → BOH → 170ms → 0.17 sec

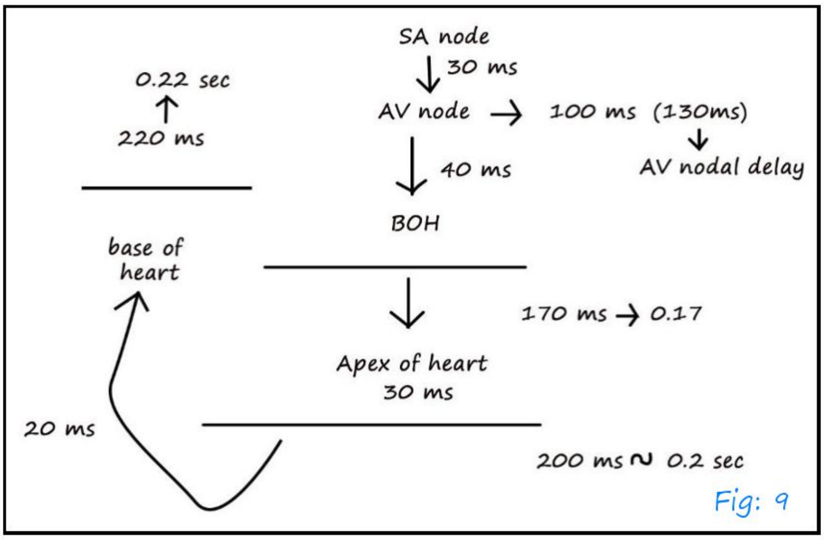
SA node
30 ms
AV node
100 ms (130ms)
AV nodal delay
40 ms
BOH
0.22 sec
220 ms
base of heart
170 ms → 0.17
Apex of heart
30 ms
20 ms
200 ms ∾ 0.2 sec

Fig: 9

- Ventricular depolarization starts from mid part of septum (left side)

  ↓

  Endocardium → Epicardium
- Last part of ventricle to get depolarized → base of heart > Upper most part of septum
- Last part of ventricle to get depolarized is the first part to get repolarized → Base of the heart
- Last part to get repolarized → first part to get depolarized → mid part of septum
- Isolated segment of ventricle

  ↓↓

  Depolarization similar to repolarization

  endocardium → epicardium

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Velocity of conduction

- Maximum velocity of conduction → Purkinje fibres
  - SA node – 0.05 m/s
  - AV node – 0.01 m/s

- BOH – 1m/sec
- Purkinje fibre – 4m/sec

  ↓

  Max – velocity because they have maximum number of gap junction
- AV node – slowest → minimum number of gap junction

- For effective filling of ventricle → AV nodal delay

  ↓

  AV node → gatekeeper of heart

- Purkinje fibre has thick diameter fiber
- AV node – thin diameter fiber
- If there is sympathetic stimulation of heart

  ↓↓

  1.Increase HR → Positive chronotropy

  2.Increase force of contraction → Positive Ionotropy

  3.Increase rate of conduction → Positive Dronotropy

  4.Increase Excitability → Positive bathmotropy

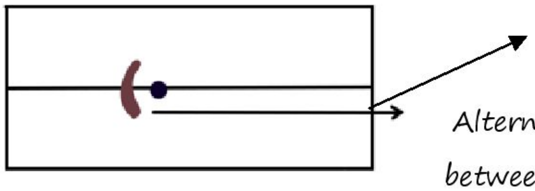
  5.Increase of relaxation → Positive Lusitropy
- Decreased refractory period
- Heart cannot be tetanized, nor can be fatigue

  ↓

  Long refractory period

  ↓

  Plateau phase because of Ca^{2+}



Bundle of kent

↓

Alternate aberrant pathway

between atrium and ventricle

↓↓

No AV nodal delay

-PR decrease

-Delta wave

↓↓

WPW Syndrome

(Wolff Parkinson white syndrome)

Fig: 10

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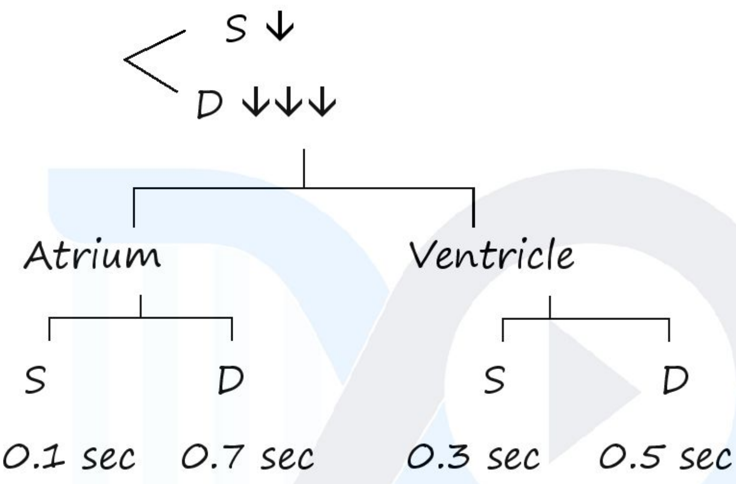
CARDIAC CYCLE

Duration of cardiac cycle 00:00:45

- Normal duration of cardiac cycle is 0.8 sec if HR is 72/min

  Exercise / HR increase = Duration decrease


S ↓
D ↓↓↓
Atrium
Ventricle
S
D
S
D
0.1 sec
0.7 sec
0.3 sec
0.5 sec

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Pressure in heart chambers 00:03:34

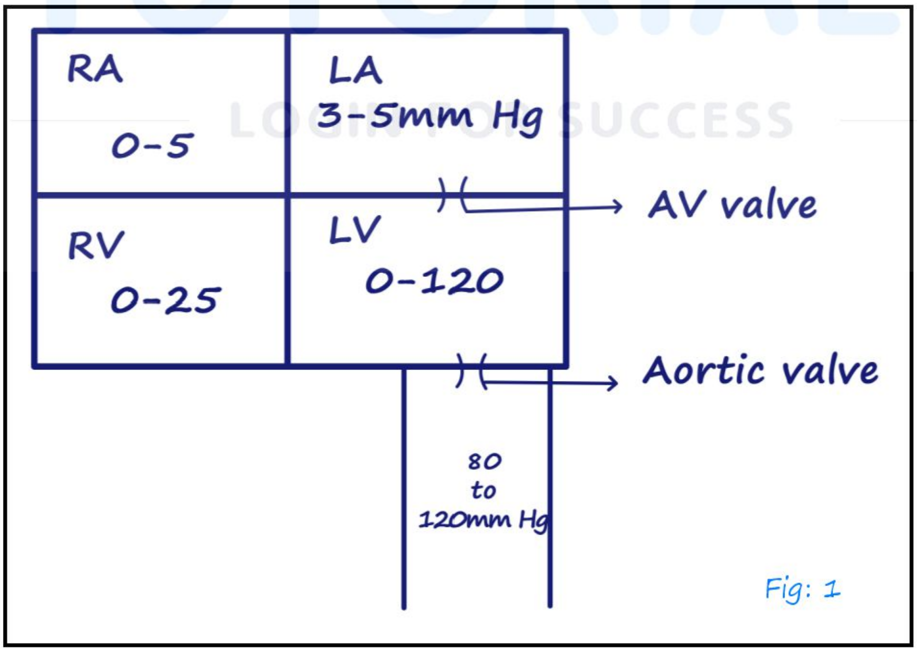
RA
0-5
LA
3-5mm Hg
RV
0-25
LV
0-120
AV valve
Aortic valve
80
to
120mm Hg

Fig: 1

Phases in systole and diastole 00:04:55

Phases

- Systole (3)
  - IVE
  - RVE
  - SVE
- Disastole (5)
  - Protodiastole
  - IVR
  - RVF
  - SvF
  - Active filling

I. Atrial contraction 00:06:18

Even before atria contract V ~ 70%

↓

V – 30%

3 mmHg → 5mmHg

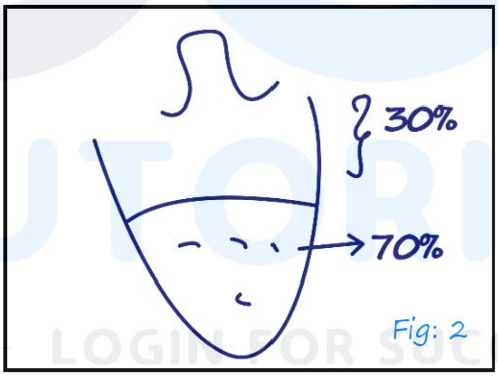

Fig: 2

Atrial contraction against rigid ventricle wall → S_4 heart sound

- Old age
- MI
- HOCM
- DCM

II.Ventricle contraction 00:09:28

Isovolumetric contraction

↓

0-80mmHg (Ventricle contracting in closed chamber)

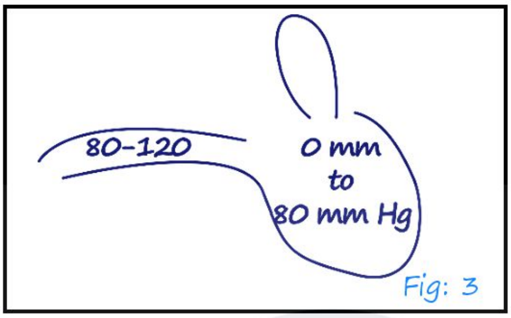

Fig: 3

AV closes → S_1 heart sound

S_1 – IVC

III.Rapid ventricular ejection 00:11:38

> 80mmHg to 120 mmHg

↓

Aortic valve – open

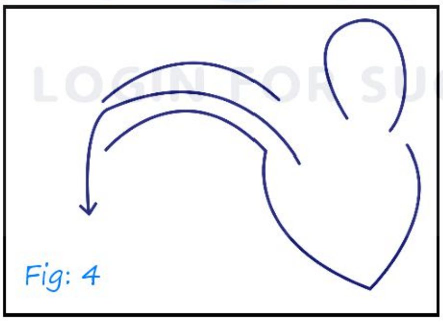

Fig: 4

IV.Slow ventricular ejection 00:13:10

- Pressure is reducing from 120 to 80mmHg
- Cause of blood flow in slow ventricular ejection is momentum of blood flow

V. Protodiastole 00:15:23

- Pressure <80mmHg

↓

Aortic valve → Close → S_2

VI.Isovolumetric relaxation 00:17:03

- Pressure < 80 to 5mmHg

↓

Ventricles are relaxing in closed chamber

VII. Rapid ventricular filling 00:17:50

- Pressure < 5mmHg

↓

AV – Open

When there is hyperdynamic circulation → S_3 heart sound

↓

1.Pregnancy
2.Anemia
3.Children
4.Athletes
5.CHF

VIII. Slow ventricular filling (Diastasis) 00:19:37

- Also known to be diastasis

Wiggers diagram 00:23:06

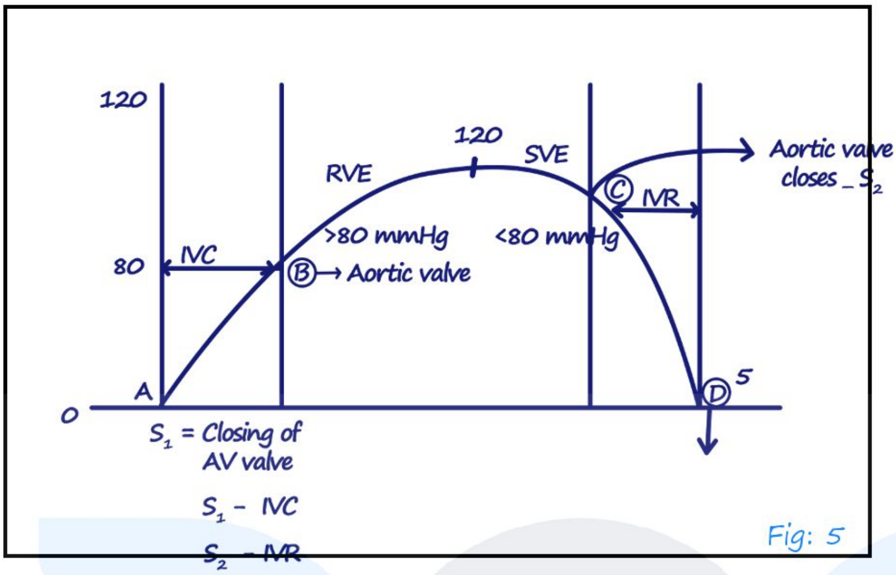
120
80
0
A
IVC
B → Aortic valve
RVE
>80 mmHg
120
SVE
<80 mmHg
C
IVR
Aortic valve closes _ S_2
D
5
S_1 = Closing of AV valve
S_1 - IVC
S_2 - IVR

Fig: 5

Differences between heart sounds 00:26:00

S_1	S_2
1. Closure of AV valve	1. Closure of aortic valve
2. Start of IVC	2. Start of IVR
3. Long duration – 0.15 sec	3. Short duration = 0.12 sec
4. Low frequency = 25-45 Hz	4. Sharp frequency = 50 Hz
5. LOUD – High amplitude	5. Soft – low amplitude

S_3	S_4
1.Passive ventricular filling (70%)	1.Active ventricular filling 30%
2.It takes 0.1 sec	2.It takes 0.1 sec
3.Inaudible	3.Inaudible
4.Audible if freq. 30H_z	4.Audible if freq. 30H_z
5.In hyperdynamic circulation • Children • Anemia • Pregnany • Atheletes • CHF	5.In atrial contraction against rigid ventricular •Old age •Acute MI

Pressure – volume loop 00:31:26

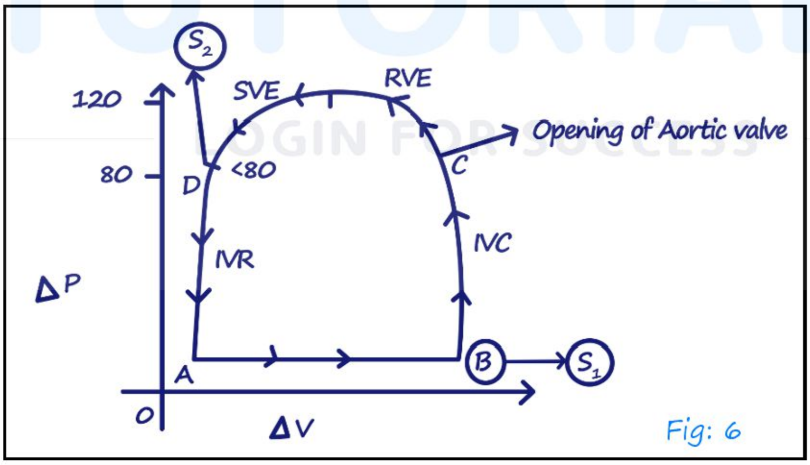
S_2
120
80
SVE
RVE
Opening of Aortic valve
<80
D
C
IVR
IVC
ΔP
A
B
S_1
O
ΔV

Fig: 6

- AB → Ventricular filling
  - 70% passive
  - 30% active

- BC → Isovolumetric contraction
- B → Closure at AV – Valve (S_1)
- Opening of aortic valve

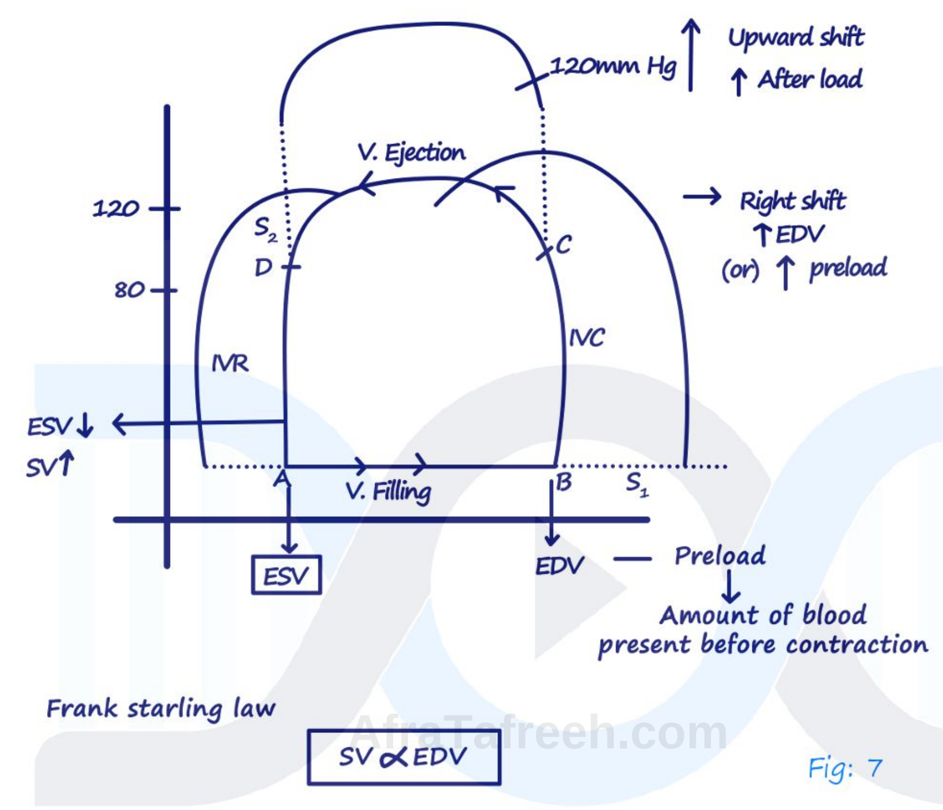
Upward shift
↑ After load
120mm Hg
V. Ejection
120
80
S_2
D
C
Right shift
↑ EDV
(or) ↑ preload
IVR
IVC
ESV↓
SV↑
A
V. Filling
B
S_1
ESV
EDV — Preload
Amount of blood present before contraction
Frank starling law
SV ∝ EDV

Fig: 7

- ESV = End systolic volume – Blood in ventricles after contraction

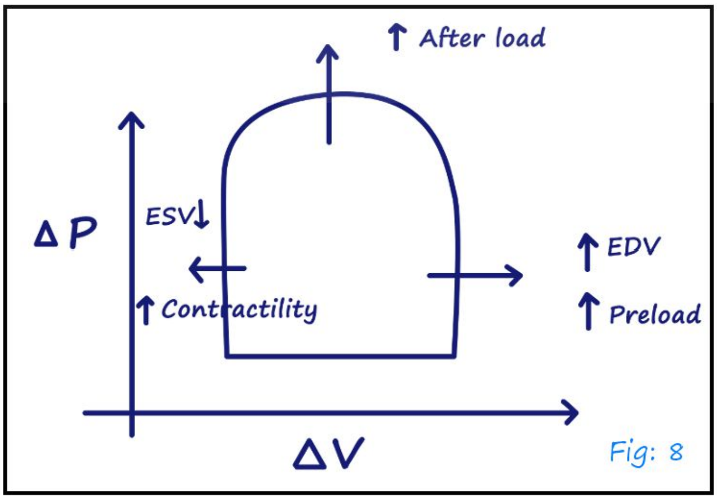
↑ After load
ΔP
ESV↓
↑ Contractility
↑ EDV
↑ Preload
ΔV

Fig: 8

- MR
  - Increase preload
  - Decrease afterload
- AS
  - Increase afterload
  - Decrease SV
  - Increase ESV
- AR
  - Increase EDV
  - Increase preload

Correlation of heart sound and ECG 00:45:15

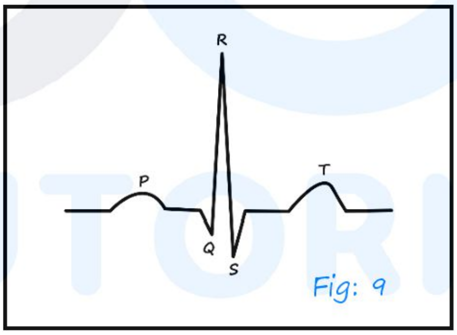

Fig: 9

- P → Atrial contraction → S_4
- (R) QRS → Ventricular contraction (IVC) → S_1
- T → Ventricular relaxation (IVR) → S_2

Clinical terminology 00:47:31

1.Electromechanical systole (QS_2)

- Period between QRS complex and closure of aortic valve

2.Left ventricular ejection time (LVET)

- Period between carotid pressure rise and closure of aorta

  [closure of aortic valve → Dicrotic notch]

3.Pre-Ejection period (PEP)

- PEP = QS_2 – LVET

  $\frac{PEP}{LVET} = 0.35$ → Correlates negatively with EF

Jugular venous pressure 00:51:08

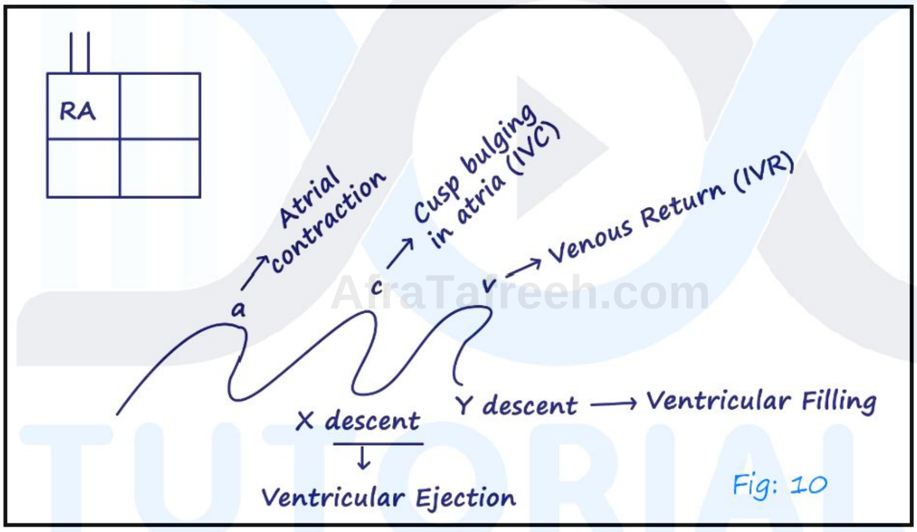
RA
a
Atrial contraction
c
Cusp bulging in atria (IVC)
v
Venous Return (IVR)
X descent
Ventricular Ejection
Y descent
Ventricular Filling

Fig: 10

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Stroke volume 00:54:22

- SV = Amount of blood ejected in 1 stroke of ventricular contraction

  = 90ml
- EDV / Preload = 130ml = Blood present before contraction
- Ejection fraction = $\frac{SV}{EDV} \times 100$ → > 65%

- $EDV = \frac{ESV}{1 - EF}$
- $ESV = EDV\,(1 - EF)$
- Cardiac output (CO) = SV X HR

  = 5.4 L/MN
- $\text{Cardiac index} = \frac{CO}{\text{Body surface area}}$

  $= \frac{5.4\ L/min}{1.7\ M^2}$

  $= 3.2\ L/min/M^2$
- Preload = EDV
- Afterload = Mean arterial pressure

  D + 1/3 (S-D)

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BLOOD PRESSURE REGULATION

- Blood pressure – lateral pressure exerted by column of blood on wall of artery
- SI unit of blood pressure – pascal
- Preferred unit – mmHg
- 2 types

Systolic BP
↓
Max. blood pressure during systole

Diastolic BP
↓
Min. blood pressure during diastole

BP = CO X Total peripheral resistance

CO ↓ Define systolic BP

Total peripheral resistance ↓ Denotes diastolic SP

CO = stroke volume X heart rate

Increase HR – systolic BP increases

- Stroke volume again depends on 3 parameters

↓ Preload → max
↓ After load
↓ Contractility

Preload
↓
End diastolic volume is max
↓
Frank – starting law

2 more terminologies

1. Mean arterial pressure → the pressure by which the heart is pumping blood into the system
2. Mean systemic pressure → the pressure by which blood enters into the heart
   - Mean systemic pressure depends upon venous return

- MAP → Average pressure in the aorta

  MAP = Diastolic blood + 1/3 X (Systolic – Diastole)

  MAP = Diastole + 1/3 X pulse pressure

  $$\text{MAP} = \frac{3\ \text{diastole} - \text{Diastole} + S}{3} = \frac{2D + S}{3}$$

- Pulse pressure depends on stroke volume and compliance of aorta

  $$\text{Pulse pressure} \propto \frac{\text{Stroke volume}}{\text{Compliance of aorta}}$$

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- When pulse pressure increases → stroke volume increases

  ↓ ↓

  - Pregnancy
  - Thyrotoxicosis

- Increase PP → Compliance of aorta decrease

  ↓

  Old age

Recording of BP

1. Seated position, after 5 minutes of rest
2. Assessed in brachial artery
3. Arm should be at the level of heart
4. Length of BP cuff → 80% of arm circumference
5. Width of BP cuff → 40% of arm circumference
6. Inflation → 30 mmHg above expected
7. Deflation → <2-3 mmHg

False high BP

- Small sized cuff
- Obesity
- Thick calcified vessel

False low Bp

- Auscultatory gap

  ↓

  In older patients, with wide pulse pressure

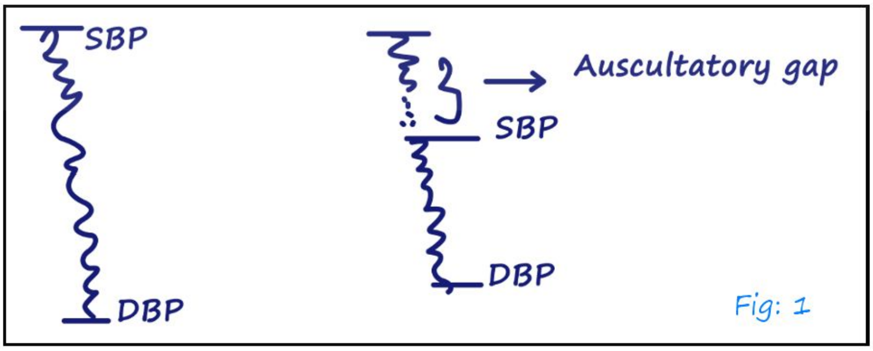

Fig: 1

- Korotkoff heart sound

  ↓

  Due to arterial turbulence on occlusion of vessel due to increase in velocity > critical velocity

Phases of korotkoff sounds

- Phase 1 – Clear tapping sound → SBP
- Phase 2 – Murmur sound
- Phase 3 – Crispy
- Phase 4 – Muffling
- Phase 5 – Disappearing of sound - DBP
- Cause of pulse → pressure wave expands the arterial wall as it travels

↓

Palpable as pulse

↓

Depends on

Stroke volume

Distension / compliance of the vessel

Regulation of BP

- 3 mechanisms

Short

Intermediate

Long term

↓

1.Baroreflex

2.Chemoreflex

3.CNS ischemic reflex

Baroreceptor High pressure baroreceptor

Carotid sinus	Aortic sinus
↓	↓
innervated by herring nerve	Innervated by CVAN Nerve
↓	↓
branch Of IX cranial nerve	branch Of X nerve

- Carotid sinus and aortic sinus respond to MAP = 70-150 mmHg (Max. BP – 180 mmHg) → always firing
- IX and X nerve also called as buffer nerve
- If BP is high → firing is high
- If BP is low → firing is low
- When firing comes from IX and X nerve

  ↓

  Gives impulse to nucleus tractus solitareus

1.

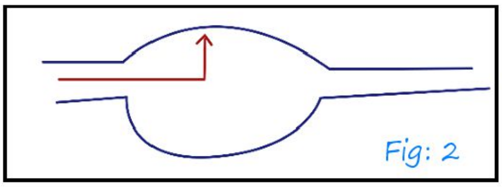

Fig: 2

If BP is high → Stretch will be more

↓

Firing also more

↓

NTS

Inhibiting ⊕ | stimulating

Sympathetic / VasoMotor Centre

CVLM
↓
Caudal ventrolateral medulla

RVLM
↓
Rostral ventrolateral medulla (main symptom centre)

Parasympathetic / cardio inhibitory / cardio vagal centre / IX nerve
↓↓
BP decreases

- GABA is released from CVLM to inhibit RVLM → decreases BP and HR
- Whenever BP is high, HR will decrease

↓↓

Marey's law → HR ∝ 1/BP

(or)

BP ∝ 1/HR

2.Whenever BP is less

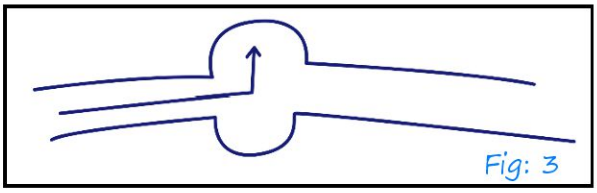
Fig: 3

Stretch is less
↓
Firing is less

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↓ stimulus to

Nucleus tractus solitus

VMC　　　　CIC / X

↓ stimulates　　↓

RVLM　　　　increase HR

3.

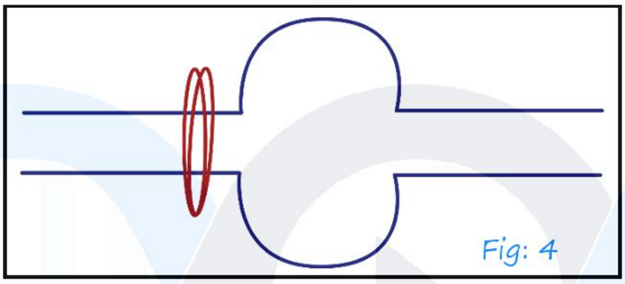

Fig: 4

- If someone had occluded proximal to carotid sinus

↓↓

Blood cannot go → Stretch will be low

↓↓　　　　↓

Increase BP　　firing would be low

Increase HR　　stimulates | Inhibits

VMC/CVLM　　CIC

- If you occlude both carotid artery

↓↓

Increase BP

Increase HR

4.If sinus is ligated distally or occlusion above carotid sinus

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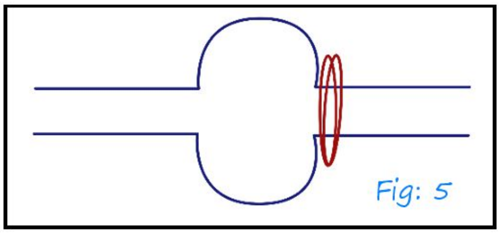


Fig: 5

- Blood is coming into sinus, but not going out → Stretch increase

  ↓↓

  BP will be less

Stretch increase

↓

Firing increase

Inhibit vasomotor center | Excite CIC / CVC/ X nerve

BP decrease

HR decrease

5.

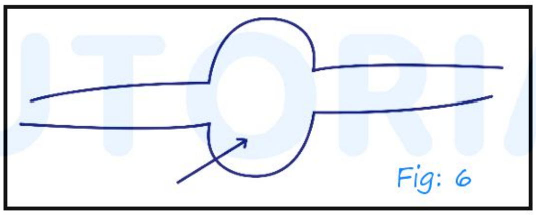


Fig: 6

- if we massage carotid sinus → Stretch is more

  ↓↓

  BP and HR decrease

Stretch is more

↓

Firing will be more

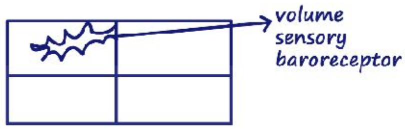
Inhibit vasomotor center | Stimulate CIC / CVC/ X nerve

- These baroreceptors are most sensitive to pulse pressure > MAP

Other baroreceptors

- Low pressure baroreceptor / volume sensing baroreceptor

↓



Increase fluid

↓↓

Increase HR

- Normal mean arterial pressure around 90-100mmHg

  Upto 60 → baroreceptor cares

  Accident → MAP < 60 mmHg

  ↓↓

  Chemoreceptor cares

  Carotid body   Aortic body

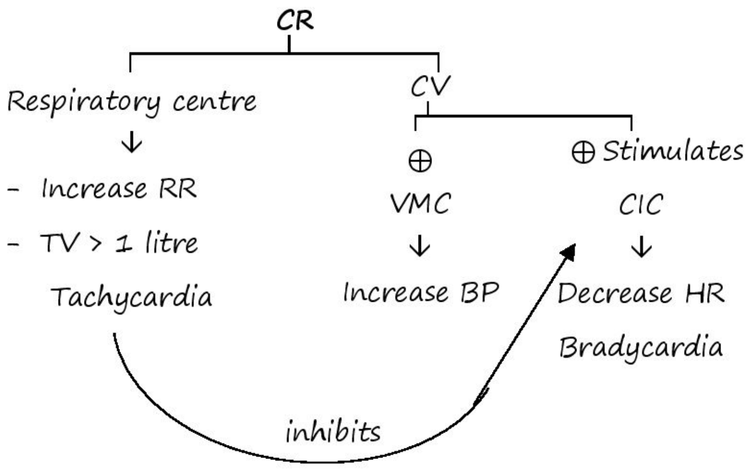
  Glomus cell

  ↓

  O_2 sensitive K^+ channel

  ↓↓

  Decrease pO_2 ⎤
  Increase pCo_2 ⎬ due to hypotension
  Acidosis ⎦


CR
Respiratory centre
- Increase RR
- TV > 1 litre
Tachycardia
CV
⊕
VMC
Increase BP
⊕ Stimulates
CIC
Decrease HR
Bradycardia
inhibits

- Chemoreceptor stimulation causes both

  Increase HR — Decrease HR

- Mild chemoreceptor stimulation → decrease HR
  Moderate / severe chemoreceptor – increase HR
  (Dominant effect)

- Chemoreceptor discharge during hypotension can cause mayer waves
  ↓
  Slow regular oscillation in arterial pulse when hypotension

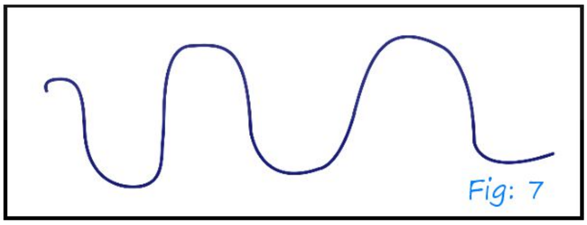


Fig: 7

Traube – herring waves → completely different from meyer wave
↓↓
Simple fluctuation of blood pressure during respiration

- MAP <30-20 mmHg

  ↓↓

  CNS will go in ischemia

  ↓↓

  CNS ischemic response

  ↓↓

  Blood flow to vasomotor centre decrease (VMC)

  ↓

  VMC is first time directly stimulated maximally due to hypocapnia

  ↓

  Most severe degree of Vaso constriction

  ↓↓

  Increase 200 mmHg

  ↓

  Last method → Last ditch stand

Chemical control of BP

- Vasoconstrictor

  1.Urotensin (Most potent one)

  2.Endothelin (Increase ET and increase pulmonary hypertension)

  ↓

  Endothelin receptor blocker

  ↓

  BOSENTAN

  3.Vasopresin

  4.V_1 receptor (G_q receptor)

  5.Nor epinephrine

  6.Angiotension II → can regulate via RAAS

Vasodilators

1. CGRP – Calcitonin gene related peptide
2. Nitric oxide
3. Natriuretic peptide
    - Atrial natrial polypeptide
    - Brain natrial polypeptide
    - CNP – C type natriuretic polypeptide

Intermediate regulation of blood pressure

1. Capillary fluid shift mechanism
2. Stress relaxation of blood vessel
3. AT – II → Varo constriction

Long term

- RAAS

  Whenever BP is low, it is sensed by juxta glomerular cell → release renin

  ↓

  Goes to liver and converts angiotensinogen to angiotensin
- In lung, there is an enzyme called angiotensin converting enzyme

  - AT I → AT II
  - Causes release of aldosterone
  - Reabsorption of sodium
  - Release of ADH
  - Thirst

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- Vasoconstriction

Q. MAP is Diastolic + 1/3rd pulse pressure

Q. Carotid sinus baroreceptor is most sensitive to pulse pressure

Q. Occlusion of common carotid arteries on both sides lead to increase HR and BP

Q. Spuriously high BP is seen in all except

A. Auscultatory gap ✓

B. Small cuff

C. Thick calcified vessel

D. Obesity

Q. Discharge from baroreceptors cause inhitrition of RVCM.

CARDIOPULMONARY REFLEXES

2 Types

Atrial wall
Or
Pulmonary artery
↓
BAIN BRIDGE
reflex

Ventricular wall
septum
↓
Bezold Jarish
reflex

Bezold – Jarish reflex 00:01:30

- Also known as coronary chemoreflex
- Response is similar to J-receptor, vasovagal syncope
- Afferents → Unmyelinated vagal – C – fiber
- In cats / Rabbits –

  Stimulated by –

  1.Serotonin
  2.Veratridine
  3.Capsaicin
  4.Phenyl biguanide
- Response

  1.BP decreases- Hypotension
  2.HR decreases- Bradycardia
  3.Apnea followed by hyperpnea (Rapid breathing)
- In humans

  1.During MI or reperfusion therapy
  2.Radio contrast – coronary angiography

3.Vasovagal syncope

- Prevention
  - Start IV fluids beforehand
  - β – Blockers
  - Epinephrine
  - Vagolytics

Bain bridge reflex

Atrial wall reflex: 00:08:45

- Atrial wall receptors – low – pressure baroreceptors

  More in right atrium (RA>>LA)
- Respond to stretch

  ↓

  Volume sensing Baro receptor
- Increase in RA filling (Stretch)

  ↓

  Response

  ↓

  1.Tachycardia (increase HR)

  2.ADH decrease — Bain Bridge Reflex

  3.ANP increase
- It is tachycardia due to right atrial stretch

  - Hypovolemic state

    ↓

    High pressure baroreceptors dominate
    - Carotid sinus
    - aortic sinus
  - Hypervolemic state

    ↓

    Bain bridge reflex

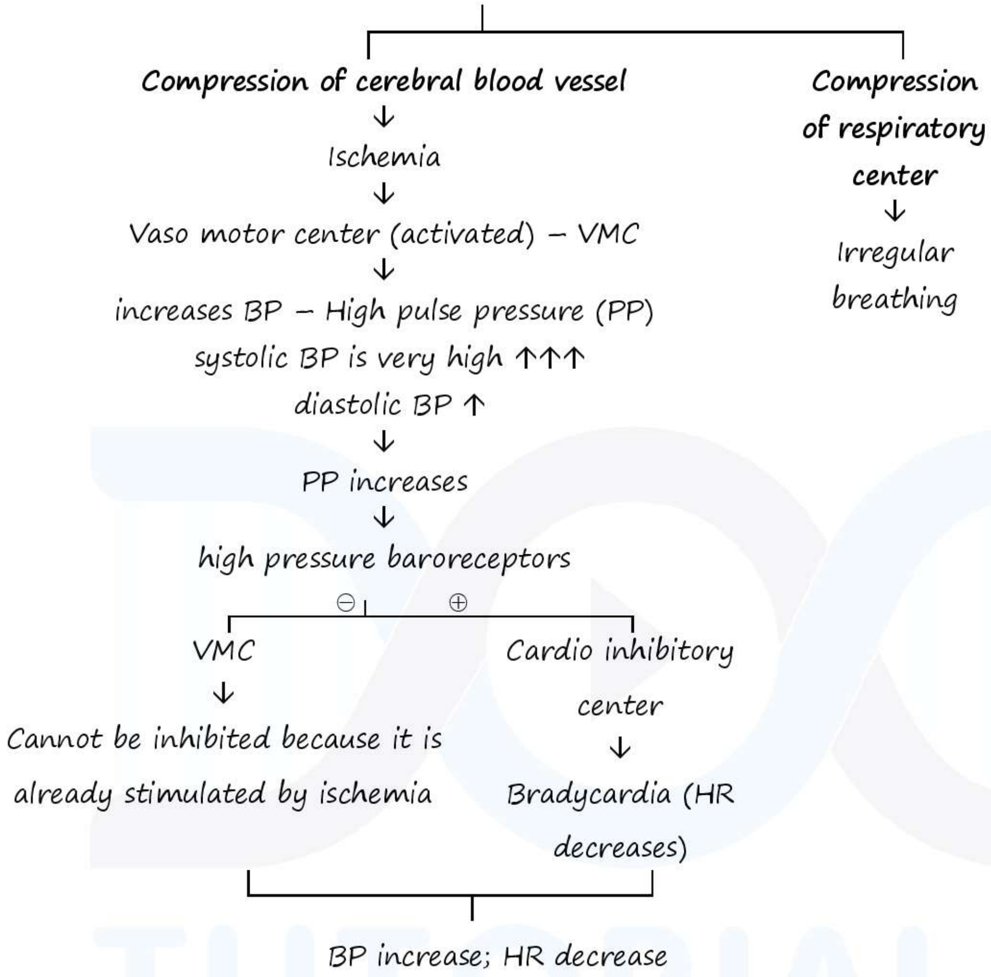
    ↓

    Low pressure baro receptors dominate

Cushing reflex/reaction 00:14:05

- Head injury

Increased intra cranial tension



Compression of cerebral blood vessel
↓
Ischemia
↓
Vaso motor center (activated) – VMC
↓
increases BP – High pulse pressure (PP)
systolic BP is very high ↑↑↑
diastolic BP ↑
↓
PP increases
↓
high pressure baroreceptors

⊖ VMC
↓
Cannot be inhibited because it is already stimulated by ischemia

⊕ Cardio inhibitory center
↓
Bradycardia (HR decreases)

BP increase; HR decrease

Compression of respiratory center
↓
Irregular breathing

Cushing triad

1. Increases BP with increase in Pulse Pressure
2. Reflex bradycardia
3. Irregular breathing

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CARDIOPULMONARY REFLEXES

2 Types

- Atrial wall Or Pulmonary artery → BAIN BRIDGE reflex
- Ventricular wall septum → Bezold Jarish reflex

Bezold – Jarish reflex 00:01:30

- Also known as coronary chemoreflex
- Response is similar to J-receptor, vasovagal syncope
- Afferents → Unmyelinated vagal – C – fiber
- In cats / Rabbits –

  Stimulated by –

  1.Serotonin

  2.Veratridine

  3.Capsaicin

  4.Phenyl biguanide
- Response

  1.BP decreases- Hypotension

  2.HR decreases- Bradycardia

  3.Apnea followed by hyperpnea (Rapid breathing)
- In humans

  1.During MI or reperfusion therapy

  2.Radio contrast – coronary angiography

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3.Vasovagal syncope

- Prevention
  - Start IV fluids beforehand
  - β – Blockers
  - Epinephrine
  - Vagolytics

Bain bridge reflex

Atrial wall reflex: 00:08:45

- Atrial wall receptors – low – pressure baroreceptors

  More in right atrium (RA>>LA)

- Respond to stretch

  ↓

  Volume sensing Baro receptor

- Increase in RA filling (Stretch)

  ↓

  Response

  ↓

  1.Tachycardia (increase HR)

  2.ADH decrease — Bain Bridge Reflex

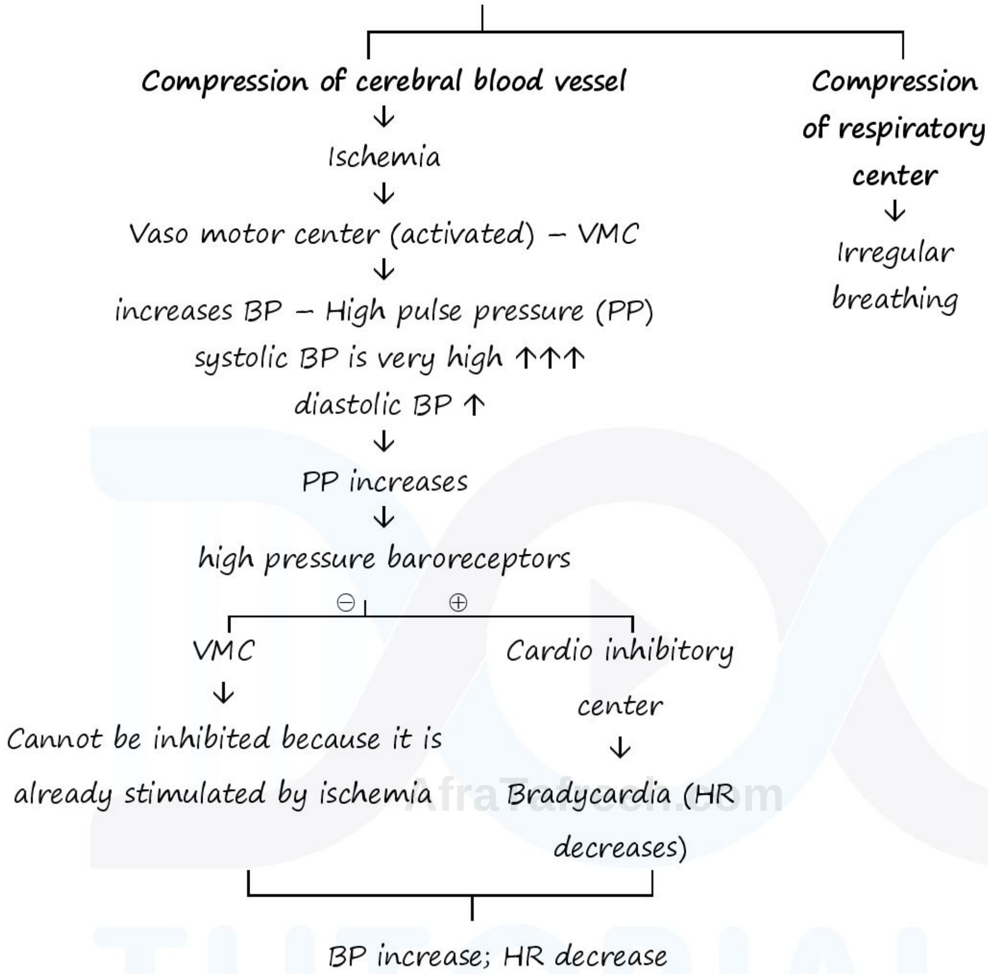
  3.ANP increase

- It is tachycardia due to right atrial stretch
  - Hypovolemic state
    ↓
    High pressure baroreceptors dominate
    - Carotid sinus
    - aortic sinus
  - Hypervolemic state
    ↓
    Bain bridge reflex
    ↓
    Low pressure baro receptors dominate

Cushing reflex/reaction 00:14:05

- Head injury

Increased intra cranial tension



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VASCULAR SYSTEM

Aorta 00:00:27

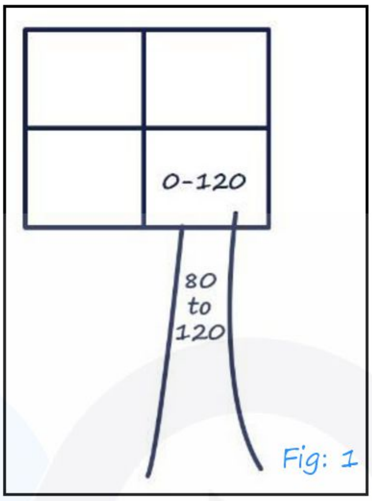

Fig: 1

- AORTA maintains diastolic pressure as 80mm Hg not zero because of its elasticity, so it is called Wind Kessel vessel.
- Elasticity is due to

  1.fibrillin protein
  - mutation of fibrillin gene causes MARFAN'S SYNDROME
  - Echocardiogram – aortic dilation at the root of aorta.

  2.Elastin protein
  - Elastin gene mutation causes supravalvular Aortic stenosis in William syndrome.
- AORTA have min cross-sectional area, has max blood flow because velocity $\alpha \frac{1}{\text{Area}}$

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Arterioles / Resistances vessels 00:04:25

- Maximum smooth muscles are present
- Contraction of smooth muscles→ severe vasoconstriction→ decreases Blood Flow and increases Resistance.
- Arterioles also decrease Resistance by causing vasodilation.

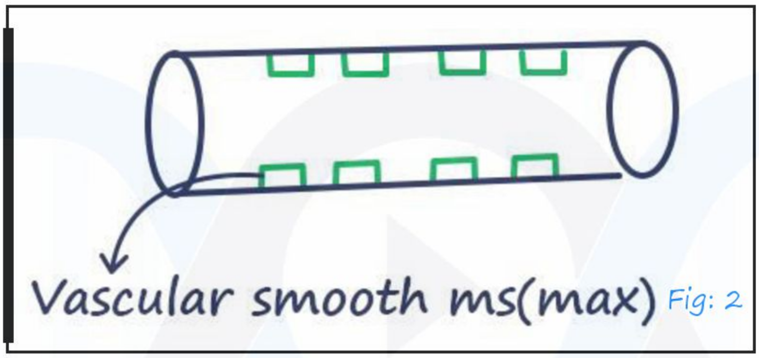


Fig: 2

Capillaries / Exchange blood vessels 00:06:21

- exchange of gases takes place here.
- It has only 5% of blood
- maximum cross-sectional area, minimum velocity &sluggish blood flow.
- Pre capillary sphincter are controlled by local metabolites.
- Capillaries undergoes intermittent contraction and relaxation (Phenomenon called as VASOMOTION)

Starling forces 00:09:26

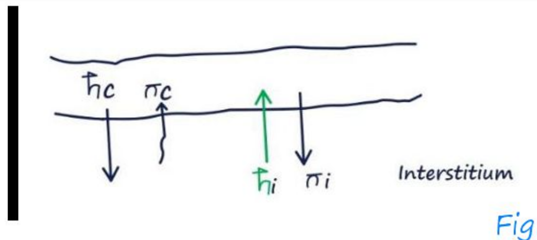


Fig: 3

- h_c – hydrostatic pressure of capillary →moves the water outside capillary
- π_c – Oncotic pressure of capillary → maintains the water in capillary
- h_i – hydrostatic pressure of interstitium
- π_i - oncotic pressure of interstitium

Net force= $(h_c - h_i) + (\pi_i - \pi_c)$

Oncotic pressure → due to Albumin
π_c – 25 mmHg
π_i - 3 mmHg

LYMPH: 00:12:03

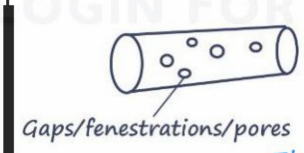
- If filtration > Reabsorption; This collection of excess fluid is lymph and it is taken back by lymphatic circulation.
- Increase in lymphatic circulation by
  - lymphatic pump
  - Contraction of muscle
  - Massaging
  - Pulsation of surrounding blood vessels

- Decrease in lymphatic circulation - decrease π

Liver disease kidney disease

- Lymphatic Obstruction - Filariasis

Three types of blood capillaries

Continuous	Fenestrated	Sinusoidal
• Most numerous • No gap junction • Seen in Brain, skin, lung, muscles	• Gaps / Fenestrations / pores Between capillary endothelium • Seen in Renal Glomerulus, Endocrine gland  Fig: 4	• Discontinuous blood capillary • Wide gap between capillary endothelium • Seen in liver, spleen, bone marrow

AhaTafreeh.com DOC TUTORIALS LOGIN FOR SUCCESS

- If no capillary between two vessels → **Arterio venous anastomosis** aka **shunt vessels**
- seen in finger, palm, ear lobe
- for temperature regulation.

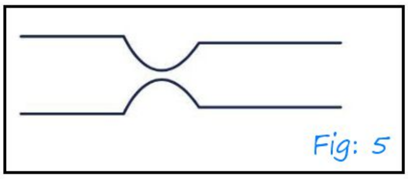


Fig: 5

Veins 00:19:23

- Veins have maximum blood content (60% of blood). So, it is called Reservoir / Capacitance blood vessels
- Orthopnea:
  - Dyspnoea in recumbent position.
  - Increase pooling blood in pulmonary circulation

Hemodynamics 00:21:07

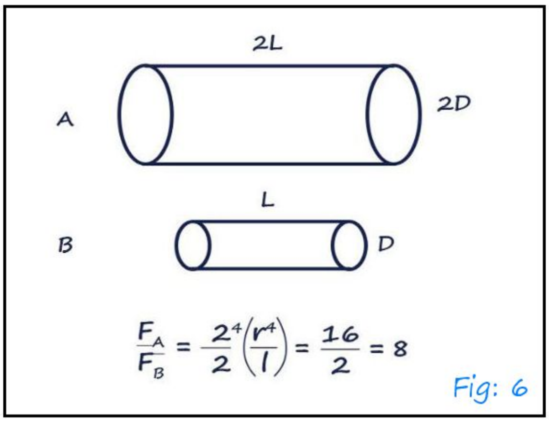
- Ohm's law → v = I X R
- Pressure = Blood Flow x Resistance
- Poiseuille Hagen Formula

$$\text{blood flow(F)} \propto \frac{\Delta P \times r^4}{l \times \text{viscosity}}$$

ΔP – change in pressure

r – radius

$$F \propto \frac{r^4}{l}$$



$$\frac{F_A}{F_B} = \frac{2^4}{2}\left(\frac{r^4}{l}\right) = \frac{16}{2} = 8$$

Fig: 6

Blood flow 00:24:24

- Reynold no. $\propto \dfrac{\text{density} \times \text{velocity} \times \text{diameter}}{\text{Viscosity (RBC)}}$
- In Anaemia- viscosity decrease, Reynold no. increases
  → Turbulent blood flow

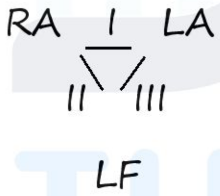
LAMINAR	TURBULENT
No Noise	Noise
Reynold number < 2000	>2000

ECG

- Electro cardio graph → Machine
- Electro cardio gram → paper
- It is the graphical representation of electrical activity of heart
- It is a summated potential

There are 12 leads

- 3 Bipolar
  - ,I, II, III
- 9 Unipolar
  - 3 Augmented ↓
    - aV$_R$
    - aV$_L$
    - aV$_F$
  - 6 chest lead ↓
    - V$_1$
    - V$_2$
    - V$_3$
    - V$_4$
    - V$_5$
    - V$_6$


RA
I
LA
II
III
LF

- aV$_R$

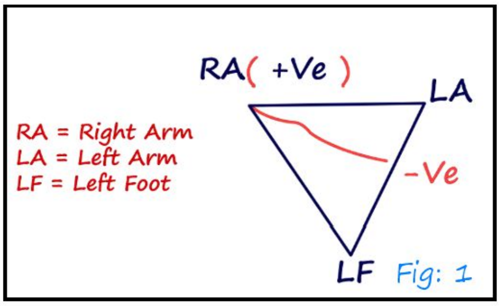

RA(+Ve)
LA
RA = Right Arm
LA = Left Arm
LF = Left Foot
-Ve
LF

Fig: 1

- aV_l

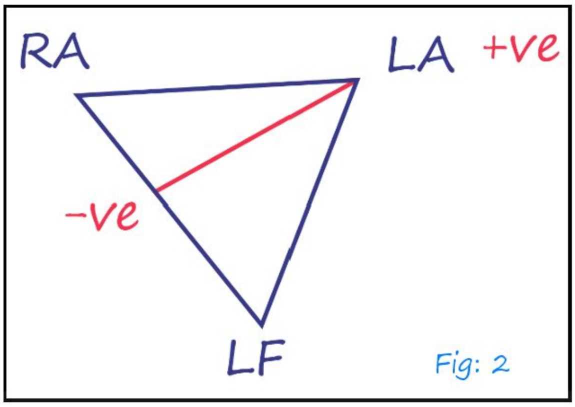

RA
LA
+ve
-ve
LF

Fig: 2

- aV_F

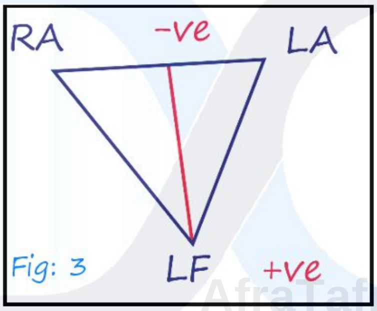

RA
-ve
LA
LF
+ve

Fig: 3

Einthoven law 00:04:20

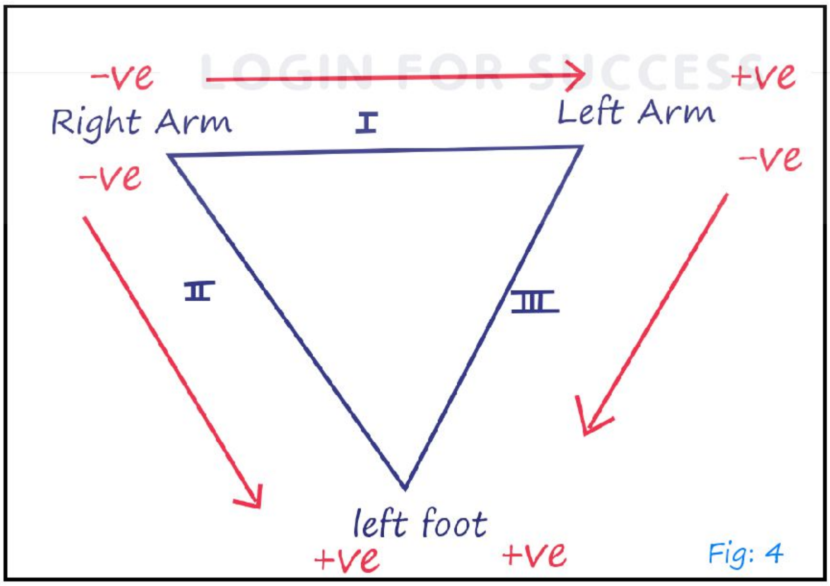

-ve
+ve
Right Arm
I
Left Arm
-ve
-ve
II
III
left foot
+ve
+ve

Fig: 4

i.e., I + III + (−II) = 0

I + III = II

- Einthoven reversed the polarity of lead II to get upward deflection
- V_1 and V_2 → Septal leads
- V_3 and V_4 → Anterior surface leads
- V_5 and V_6 / aV_L and I → Lateral surface leads

  II, III, Av_F → Inferior surface leads

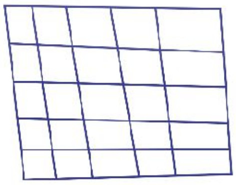
  Av_R → Cavity of heart.

Heart

- Inferior Surface → Corresponds To Right Coronary Artery
- Lateral Surface → Left Circumflex Artery
- Septal And Anterior Surface → Left Anterior Descending Artery

ECG Paper 00:10:40

- 1 big square (BS) = 25 small squares (SS)



  1 small square ≃ 0.04 seconds

  1 big square ≃ 0.04 x 5 = 0.2 seconds

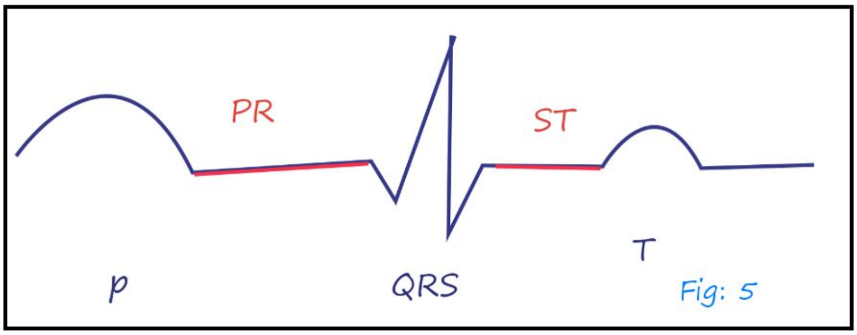


Fig: 5

- Wave – Any deflection in ECG paper is a wave
- Segment – Straight lines (Isoelectric lines) eg: PR, ST
- Interval – Wave + Segment

  Eg: PR interval = P wave + PR segment

  QT interval + QRS + ST segment + T wave
- P. Wave → Signifies Atrial depolarization
- QRS → Signifies ventricular depolarization [Atrial repolarization is marked]
- T → signifies ventricular repolarization

P Wave 00:14:56

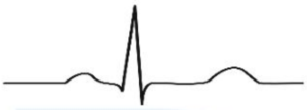
- It has 2 ½ small squares
- i.e., 2.5 x 0.04 – 0.1 sec. (0.08 – 0.12)

  amplitude – 0.25MV
- Tall P wave → P. Pulmonale → Right atrial enlargement
- Wide P wave → P Mitrale → Left atrial enlargement
- Absent P wave → Atrial fibrillation

PR interval 00:17:30

- P wave + PR segment
- Signifies AV nodal delay

Short → WPW Syndrome	Prolonged
delta P wave	Heart block
	AV Block



Degrees of heart block: 00:19:10

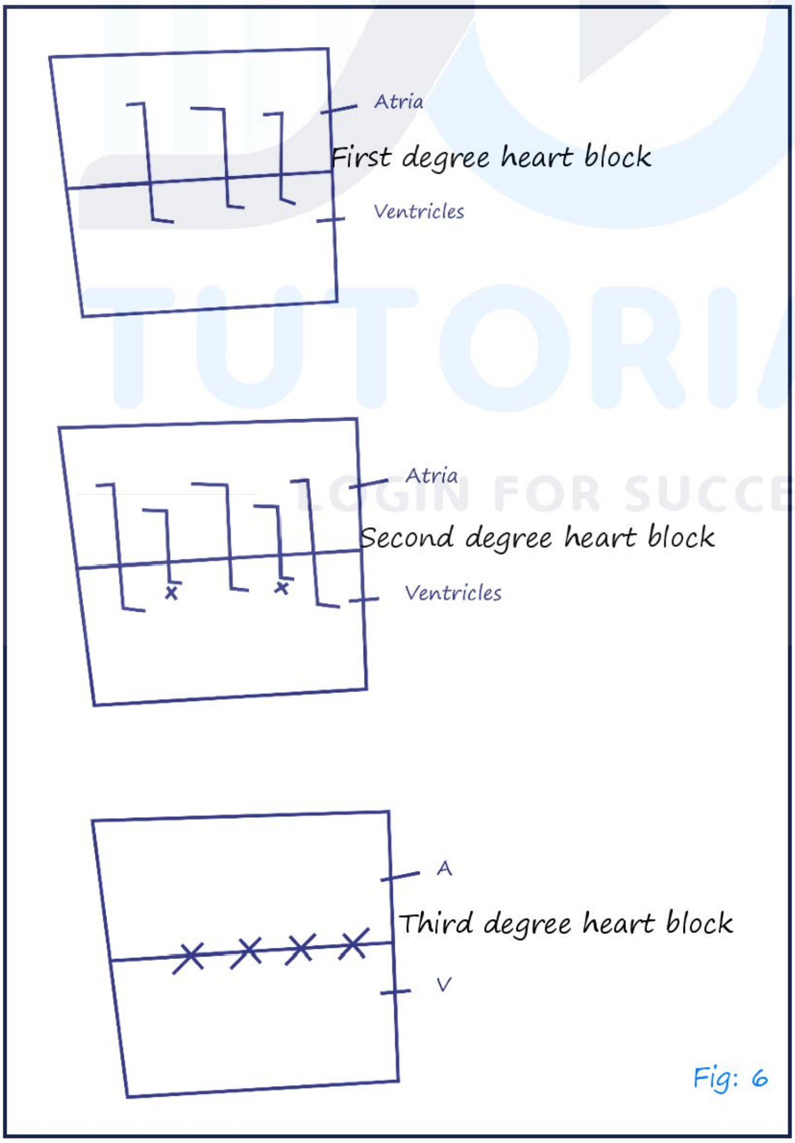
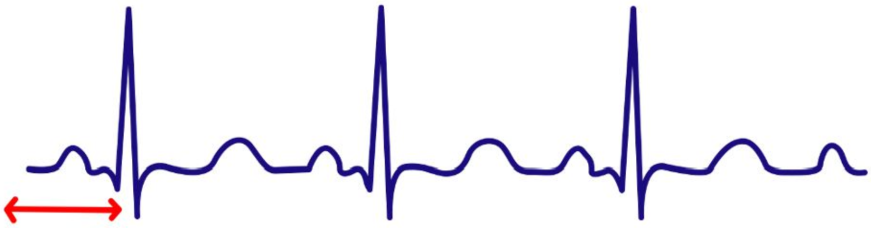

Atria
First degree heart block
Ventricles
Atria
Second degree heart block
Ventricles
A
Third degree heart block
V

Fig: 6

First degree heart block



PR Interval – Prolonged (>0.2 sec)

Every P Wave is followed by QRS

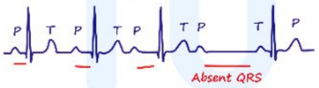
Fig: 7

Second degree heart block

mobiz – I

↓

Wencke back phenomenon


P
T
P
T
P
T
P
T
P
Absent QRS

progressive increase in PR interval until one P wave drop

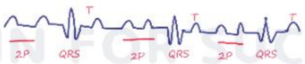
mobiz – II

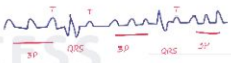
2:1

- 2 P wave
- 1 QRS

3:1

- 3 P wave
- 1 QRS


T
T
T
2P
QRS
2P
QRS
2P
QRS


T
T
T
3P
QRS
3P
QRS
3P

Third degree heart block

- Atrio-ventricular dissociation
- Heart rate - <30,20.

↓

STOKE ADAM Syndrome

RR – Interval 00:27:40

- It is between successive R waves
- Calculate heart rate (HR)

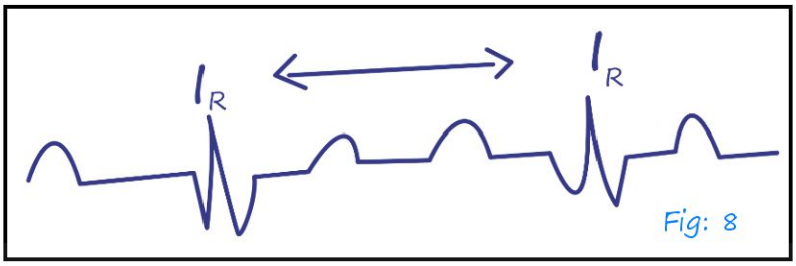


Fig: 8

$$HR = \frac{1500}{\text{Number of small squares between 2 R waves}}$$

$$\text{Normal HR} = \frac{1500}{20} = 75/\text{min}$$

QT Interval: –

- QRS + T
- Ventricular depolarization + Ventricular repolarization

$$\text{Bazett formula} = QT_c = \frac{QT}{\sqrt{RR}}$$

- 0.4 sec

T Wave: -

- Significant in Hypo, hyperkalemia

Hyperkalemia	Hypokalemia
↓	↓
Tall tented T wave	Inverted T wave
P → Absent	STUPRT
QRS → Wide	ST → Depression
T → Tall	U → U wave
	PR → decreased
	T – inverted

His bundle ECG: -

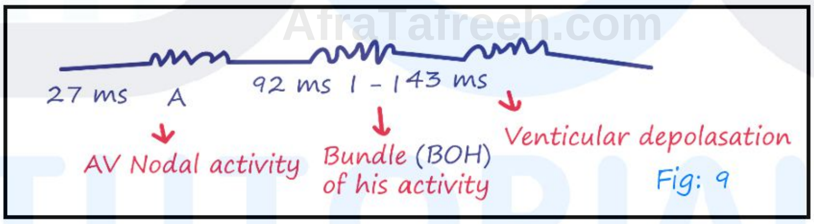

27 ms
A
92 ms
1 - 143 ms
AV Nodal activity
Bundle (BOH) of his activity
Venticular depolasation

Fig: 9

- PA → Between P wave and A wave
- AH → between AV node and BOH
- HV → Between BOH to ventricular depolarization
- If AH increase → Block is above

  HV increase → Block is below (Bundle branch block)

CARDIAC OUTPUT

- Blood pressure = cardiac output x total peripheral resistance (TPR)

↓

Increase stroke volume x Heart rate

Increase Preload	Decrease after load	Increase Contractility
EDV	MAP	

Frank starling law

- Stroke volume directly proportional to End diastolic volume(EDV)

Cardiac output

No change	Increase	Decrease
• Sleep • Moderate increase in temperature	• Anxiety • Excitement • Eating • Exercise • T temperature of environment • Pregnancy • Epinephrine	• Sitting (or) standing from lying • Kidney Amputation ↓ Increase TPR ↓ Decrease SV ↓ Decrease CO

TUTORIALS LOGIN FOR SUCCESS

Coronary blood flow

- Heart receives 5 % CO ~ 250 ml/min during diastole
- During systole coronary artery compressed

↓

Most susceptible

↓

Subendocardial region

↓

More prone to ischemia damage

- Coronary is controlled by
  - Nervous system – very little
  - Local control – due to accumulation of

a) Adenosine

b) NO

c) K+/H+/lactic acid

TUTORIALS
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Measurement of cardiac output

- Best – Fick's principle– $\left[Co= \frac{O_2 \text{ consumption}}{\text{Arterial } O2 - \text{venous } O_2} \right]$
- Dye-dilution method
  - Indocyanin green dye
  - Based on STEWART HAMILTON method
- Thermodilution
  - Cold saline
  - Based on STEMWART HAMILTION principle
- Echocardiography /Doppler
- MRI

Shock

- Hyoperfusion of tissue
- Decrease CO→ cardiogenic shock

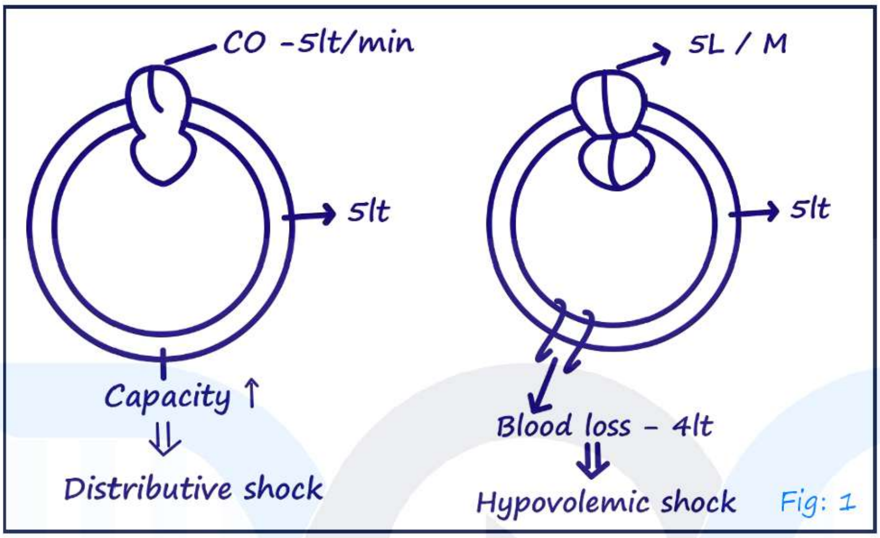
CO -5lt/min
5lt
Capacity ↑
Distributive shock
5L / M
5lt
Blood loss - 4lt
Hypovolemic shock

Fig: 1

I. Hypovolemic shock

Hemorrhage

↓↓

i. Compensatory stage
- Baroreceptors
- Chemoreceptor
- CNS ischemic reflex

- Constriction of apparent arterioles =

Decrease GFR

Decrease RPF

ii. Progressive stage

- Death is investible without treatment
- Decrease coronary blood flow

↓↓

positive feed back

↓↓

TUTORIALS LOGIN FOR SUCCESS

Cardiac determination → clot formation is small blood vessel

↓↓

decrease flow to heart

iii. Irreversible stage

- Death is inevitable even with treatment
- Cellular damage of energy – decrease ATP

  Decrease CP

II. Cardiogenic shock

- Decrease CO

III. Neurogenic shock

- On general anesthesia /spinal anesthesia

  ↓

- Decrease sympathetic NS

  ↓

- Vasodilation

  ↓

- Blood return to heart decrease – decrease CO

] – Distributive shock

IV. Anaphylaxis – shock

- Histamine → increase cell permeability → vasodilation

  ↓

  Decrease CO

V. Septic shock

- Fever – decrease CO
- Transfusion reaction – Distributive shock

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TUTORIALS LOGIN FOR SUCCESS

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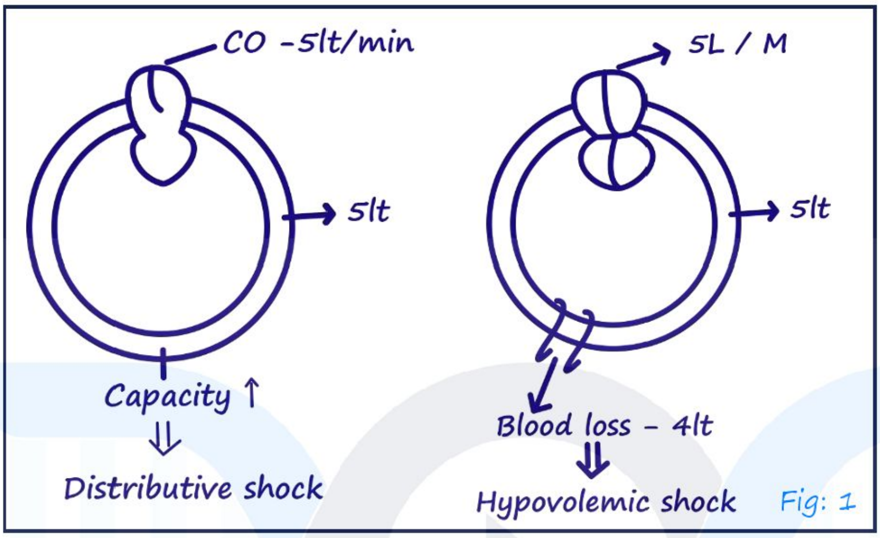
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⇓
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↓↓

positive feed back

↓↓

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↓↓

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- Cellular damage of energy – decrease ATP

Decrease CP

II. Cardiogenic shock

- Decrease CO

III. Neurogenic shock

- On general anesthesia /spinal anesthesia

↓

- Decrease sympathetic NS

↓

- Vasodilation

↓

- Blood return to heart decrease – decrease CO

(Decrease sympathetic NS, Vasodilation – Distributive shock)

IV. Anaphylaxis – shock

- Histamine → increase cell permeability → vasodilation

↓

Decrease CO

TUTORIALS LOGIN FOR SUCCESS

V. Septic shock

- Fever – decrease CO
- Transfusion reaction – Distributive shock

BLOOD COAGULATION

Blood coagulation 00:00:10

- Blood coagulation

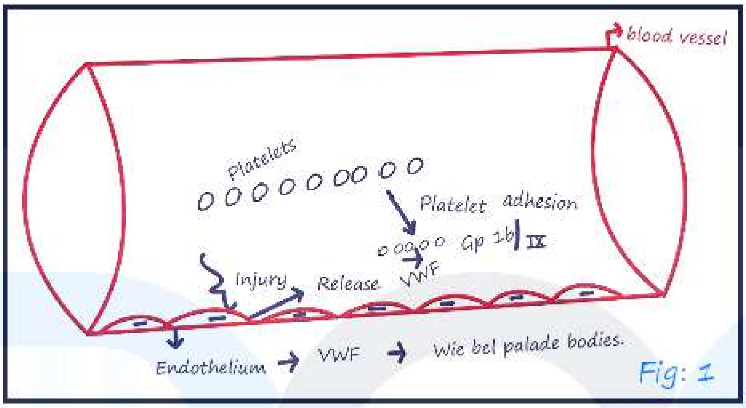

blood vessel
Platelets
Platelet adhesion
Gp 1b | IX
Injury
Release
VWF
Endothelium → VWF → Wie bel palade bodies.

Fig: 1

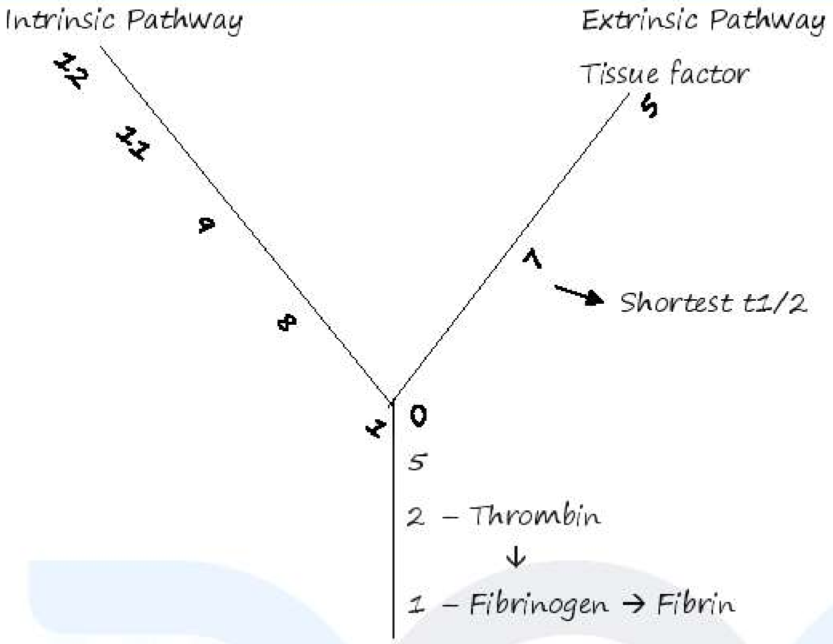
- Other locations of VWF → Megakaryocyte and liver
- For platelet adhesion → VWF and GpIb/IXa
- More platelet are attracted by Gp 2b/3a which is described as platelet aggregation
- Time since injury to primary platelet plug is bleeding time
- Immediate reaction

  Injury → Serotonin is released (From platelets) → vasoconstriction
- If damage to Ib/IXa or platelet adhesion defect it is called → Bernard Schwallier disease.

  2b/3a → platelet aggregation defect → Glanzmann Thrombusthenia

DOT TUTORIALS
LOGIN FOR SUCCESS

Coagulation cascade 00:07:40


Intrinsic Pathway
Extrinsic Pathway
Tissue factor
12
11
9
8
5
7
Shortest t1/2
1
0
5
2 – Thrombin
1 – Fibrinogen → Fibrin

Any problem in Intrinsic pathway there is increase in PTT | Any defect in extrinsic pathway there is increase in PT

- Vitamin K – dependent factors – II, VII, IX, X
- After fibrin formation

  1° PP → 2° PP or definitive PP

TUTORIALS LOGIN FOR SUCCESS

Bernard schwalier disease 00:13:05

- Deficiency of Gp Ib/IXa → Platelet adhesion defect
- Autosomal recessive disorder

  Lab parameters: BT increases and PT, PTT – Normal

  Platelet aggregation test – (A|C|E)

  ↓

  ADP | Collagen | epinephrine

  Initiate Aggregation

  If PAT is positive → Normal
- Ristocetin adhesion test (RAT) → positive – normal

  In BSD → RAT → negative

Von – Wellibrand disease 00:17:40

- Has many subtypes – but Type 1 – most common
- Has all types of inheritance – but autosomal dominant M/c)

  VWF

  - Platelet adhesion
  - Stabilizes factor VIII

  Lab parameter

  - BT ↑↑
  - PT – Normal
  - PTT - ↑↑ (VWF – Stabilizes VIII)

  PAT → Positive – normal

  RAT → negative

Glanzmann thromboesthenia 00:20:33

- Mutation is at → Gp 2b/3a
- Aggregation defect

  Lab parameters → BT ↑↑ and PT/PTT – normal

  PAT → Negative → Abnormal

  RAT → Positive → Normal

Anticlotting mechanisms / Anti coagulation Mechanisms

00:22:55

In vivo

1.Smoothness of endothelium

2.Glycocalyx layer on endothelium

3.Thrombin and thrombomodulin

Activate protein C and S
↓
Inactivate V/VIII

Activate tPA
↓
Tissue Plasminogen activator

Plasminogen → Plasmin

4.Anti-thrombin III + Heparin
↓
Inactivate IX, X, XI, XII.

BLOOD COAGULATION

Blood coagulation 00:00:10

- Blood coagulation

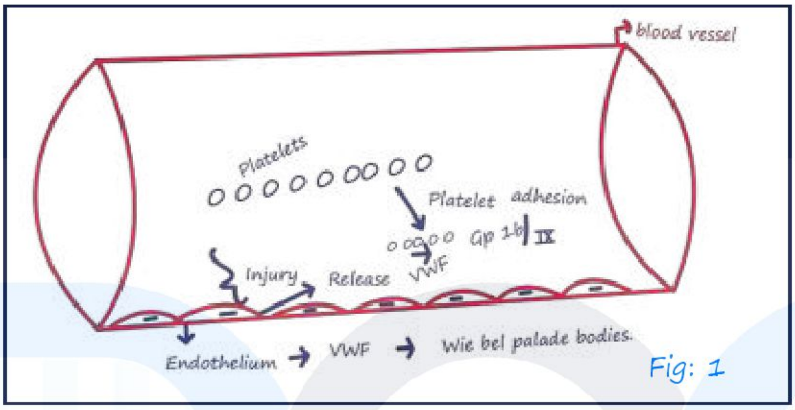

blood vessel
Platelets
Platelet adhesion
Gp 1b | IX
Injury
Release
VWF
Endothelium → VWF → Wie bel palade bodies.

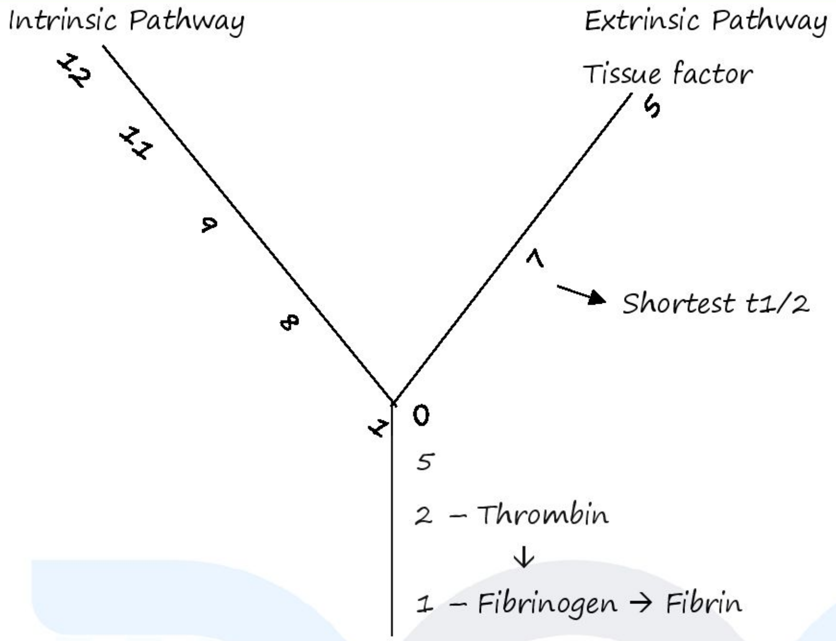
Fig: 1

- Other locations of VWF → Megakaryocyte and liver
- For platelet adhesion → VWF and Gplb/IXa
- More platelet are attracted by Gp 2b/3a which is described as platelet aggregation
- Time since injury to primary platelet plug is bleeding time
- Immediate reaction

  Injury → Serotonin is released (From platelets) → vasoconstriction
- If damage to Ib/IXa or platelet adhesion defect it is called → Bernard Schwallier disease.

  2b/3a → platelet aggregation defect → Glanzmann Thrombusthenia

Coagulation cascade 00:07:40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BLOOD CELLS

Blood

Plasma 55%   Cells 45%

↓

Synthesized by liver ← proteins : 7 to 8 g %

Except gamma globulin

Albumin	Globulin	Fibrinogen
4g%	2g%	0.2 to 0.4g %

- Normal Albumin/Globulin ratio: 1.7 to 2

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Exerts colloid osmotic pressure

Globulin:

α, β] Transport proteins eg. Cu^{+2} → ceruloplasmin

λ → gamma globulin / Immunoglobulin

RBC 00:03:33

- Size: 8 microns
- Shape: Biconcave

  Non motile/ Non nucleated
- Synthesis:

  1st trimester: yolk sac

2^{nd} trimester: liver

3^{rd} trimester: bone marrow

After birth: long bones

Flat bones

Pleuripotent Haemopoietic 00:05:00

Stem cells

Myeloid series

Lymphoid series

Colony forming unit

CFU-E

↓

Proerythroblast

↓

Normoblast

- Early
- Intermediate (Acidophilic) Hb begins to appear
- Late

↓

Reticulocyte (0.2-2%)

↓

RBC (Takes 7 to 9 days)

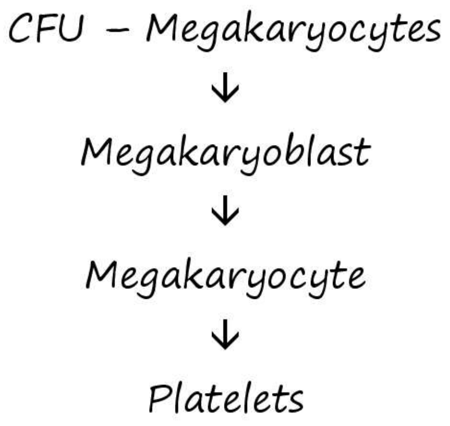
CFU – Megakaryocytes

CFU – GM

Granulocytes

Monocytes

DOC TUTORIALS
LOGIN FOR SUCCESS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Megakaryoblast
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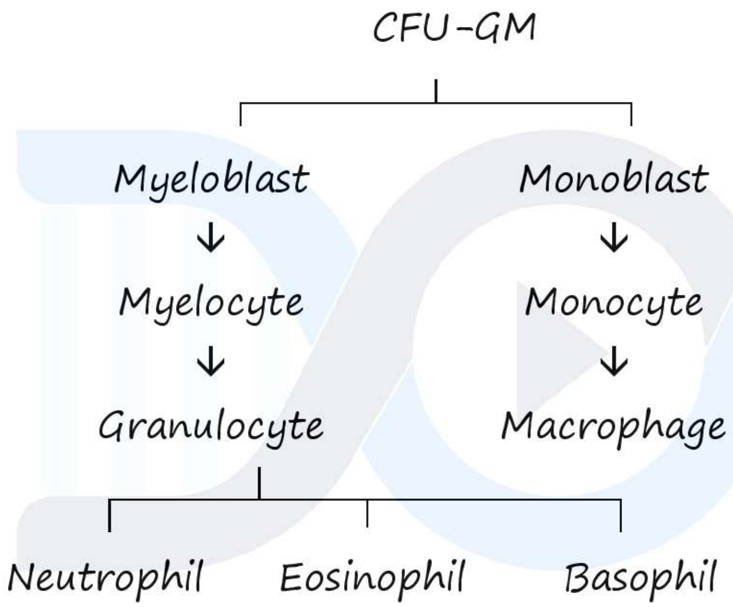
CFU-GM
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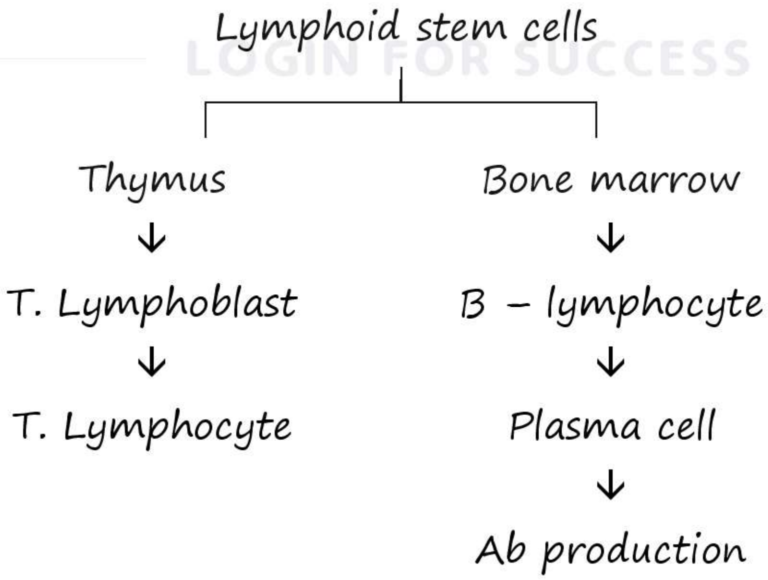

Lymphoid stem cells
Thymus
T. Lymphoblast
T. Lymphocyte
Bone marrow
B – lymphocyte
Plasma cell
Ab production

Haemopoiesis 00:09:55

i. Hypoxia: most potent stimulant

∴ Interstitial cells of kidney produce Erythropoietin (EPO)

ii. Estrogen: Inhibits erythropoiesis

iii. Testosterone: Stimulates erythropoiesis

WBC 00:11:20

WBC

Granulocyte ↓
- Neutrophil (50-70%)
- Eosinophil (1-4%)
- Basophil (0-1%)

Agranulocytes ↓
- Monocyte (2-8%)
- Lymphocyte (20-30%)

I. Neutrophil

- First to come at site of infection
- They contain lysozyme, protease, myeloperoxidase, superoxide dismutase, H_2O_2.
- Lobes

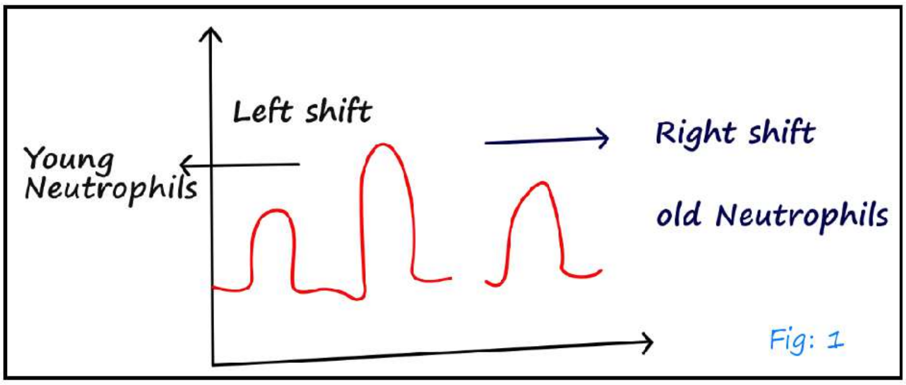
  Single lobe: 5%

  Two lobe: 15%

  Three lobes: 35-45%

  Four lobes: 15%

  Five lobes: 5%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Young Neutrophils
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old Neutrophils

Fig: 1

II. Monocyte

- Next to come to site of infection
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- Transform into macrophages – APC (Antigen Presenting Cell)
- These are largest WBC (18 μ)

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T lymphocyte → cell mediated immunity

B lymphocyte → Humoral immunity

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Antibody secretion

IgA → maximum in secretions

IgG

IgM

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Provides mucosal immunity in – GIT

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1. They have antiallergic role
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Blood groups 00:24:37

- M & N system can be used for paternal dispute.

ABO

Blood group	Antigen	Anitbody	
A	A	Anti B	[Antibodies are produced due to other antigens which enter blood via GIT in fetal life]
B	B	Anti A	
AB	AB	No antibody	
O	O	Anti A & Anti B	

Rh

- cC, dD, eE
- >90% D
- Anti D Antibody is present only if Rh negative person is exposed to Rh positive blood.

  Eg: Erythroblastosis fetalis

  - Mother Rh negative
  - Fetus Rh positive

  ∴ Anti D Ab given within 72 hrs.

Blood Indices 00:29:50

i. Pack cell volume/ Hematocrit – 40-46% (approx.)

- Decreases in anemia
- Increases in polycythemia

ii. Mean corpuscular volume: $\frac{\text{PCV}}{\text{RBC count}}$ = 80 – 95 fl

MCV > 100 – Macrocytes

iii. Mean corpuscular Hemoglobin (MCH) -

$\frac{\text{Hb}}{\text{RBC count}}$ = 28-32 pg

It decreases in iron deficiency anemia

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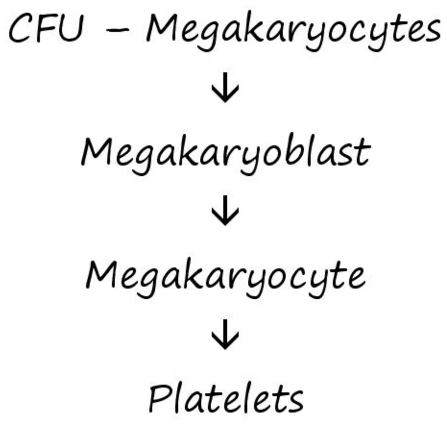
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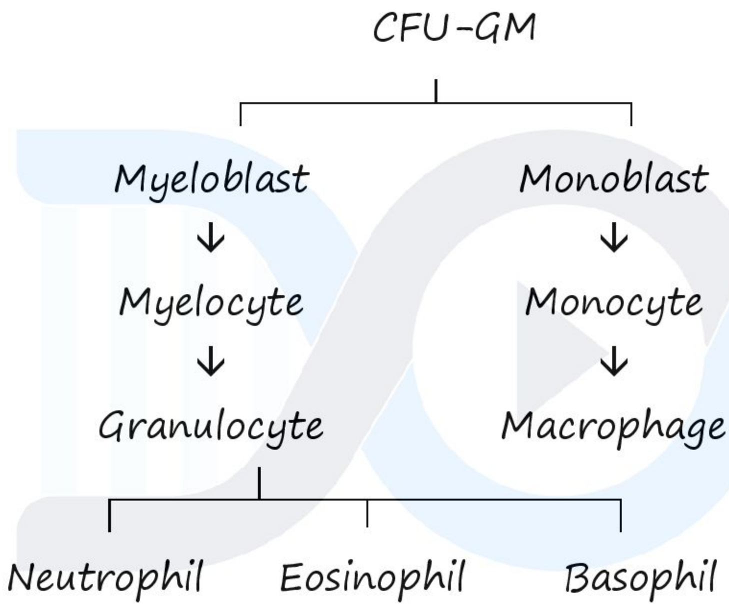
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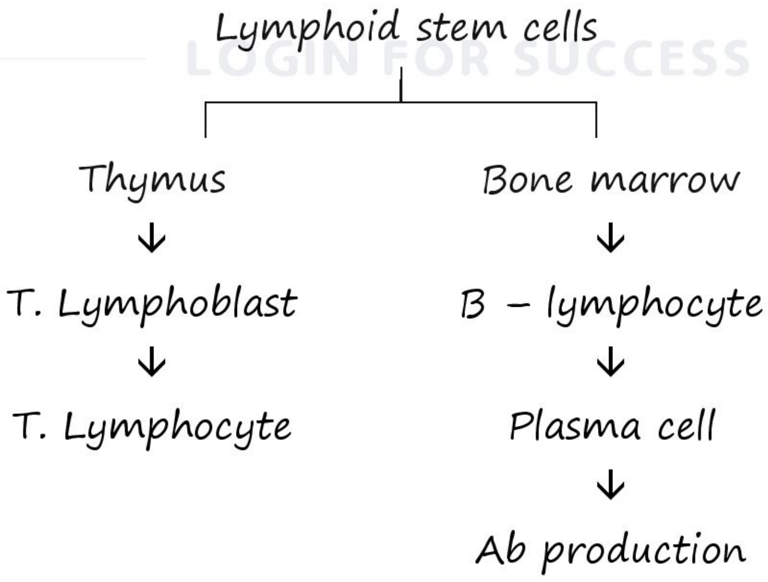
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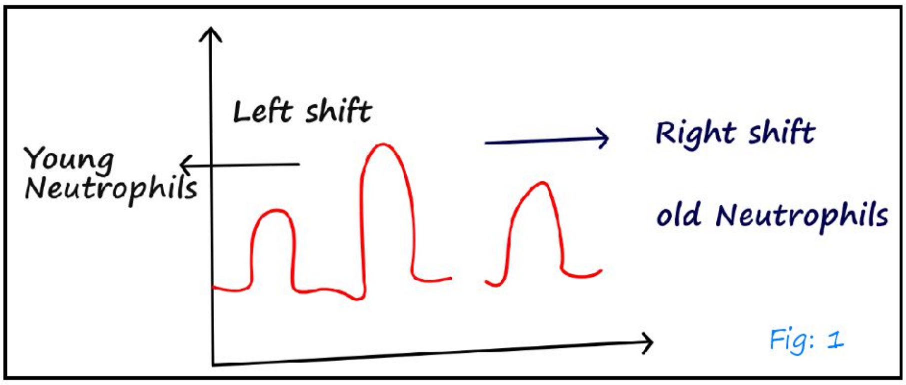
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STRUCTURE AND FUNCTION OF LUNG

Respiratory physiology

Parenchyma

↓

Restrictive Lung Disease

Airway

↓

- Obstructive lung disease
- 23 generations – Wiebel Model
- 16 generations – conducting airway
  "Trachea to Terminal Bronchiole"
  Also known as Anatomical Dead Space
- 7 generations – Respiratory airway
  respiratory Bronchiole to Alveoli
  Also known as Exchange Airway / Alveolar Airway

Conducting Airway 00:04:26

- Measurement: Single breath nitrogen test / fowler method
- Lining epithelium: Pseduostratified ciliated columnar epithelium

↓

Move sputum towards nasopharynx

[Metachronism: Synchronized retrograde movement of cilia towards nasophyarynx]

- DYNEIN → Kartagener syndrome / immotile cilia syndrome
- Embryology: Rotation of internal organs is due to cilia

Recurrent infections -

1.Sinusitis
2.Bronchiectasis
3.Situs inversus

TRIAD of Kartagener
+
Infertility

1.Cystic fibrosis: Cilia can't move, due to thick mucus

↓

Mutation: CFTR (Chloride channel)

→ ["cystic fibrosis transmembrane regulator"]

"F (508) → Phenylalanine"

Doc: Chloride channel opener: IVACAFACTOR.

Mucolytics – N acetyl cysteine

β_2 Agonists – Salbutamol

2.Stem cells

i. Clara cells
ii. Basal cells

Regeneration

3.Smooth muscle

Bronchodilation
(Sympathetic System)
Decrease Airway Resistance
↓
β_2 receptors

1. B_2 agonists -salbutamol
2. NO
3. VIP

Non adrenergic
Non cholinergic agents

Bronchoconstriction
(Parasympathetic)
Increase Resistance
↓
Example:

1. Acetylcholine / methacholine (Anticholinergic - ipratropium bromide –cause bronchodilation)
2. Histamine: Fexofenadine, cetirizine
3. Leukotrienes (Most potent)

Type 1	Type 2
• Exchange of gases	• Surfactant producers
• Large surface area	• Progenitor stem cells, can produce type 1 cells
• Fluid transporter (Aquaporin V)	• Also known as granular cell

Surfactant:

- Appears from 28th week to 32 week of gestation age in amniotic fluid
- It is a lipoprotein

1. Dipalmitoyl Phosphatidyl choline / Lecithin → Major lipid	1. Surfactant protein A + D – Important for innate immunity
2. Sphingomyelin If L/S > 2 then lung is matured ↓ Shake Bubble Test	2. Surfactant protein B + C – form monofilm of surfactant

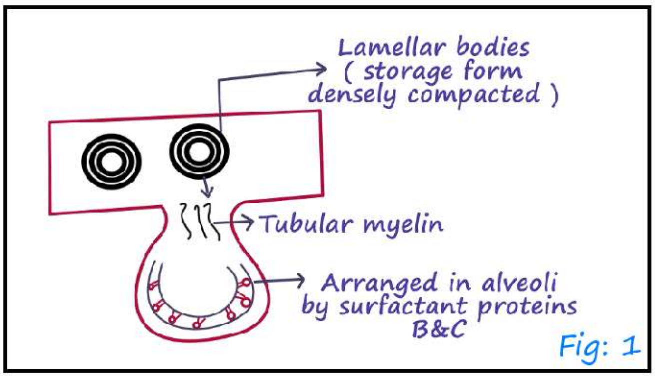
Lamellar bodies (storage form densely compacted)
Tubular myelin
Arranged in alveoli by surfactant proteins B&C

Fig: 1

Functions

- Decreases surface tension thus prevent collapse of alveoli
- It decreases collapsing pressure (laplace law $p = 2T/r$)

  ↓

  By breaking H_2o structure in alveoli
- It increases surface area
- It decreases work done
- It prevents pulmonary edema

Note: Surfactant absense → RDS

Factors

Increasing Surfactant	Decreasing surfactant
1. Steroids: Betamethasone > Dexamethasone	1. Increase insulin in Type 2 DM in GDM – can lead to hyaline membrane disease in fetus Treatment: Surfactant
2. T_3, T_4	

Note: smooth muscle is maximum relative to wall thickness in terminal bronchiole.

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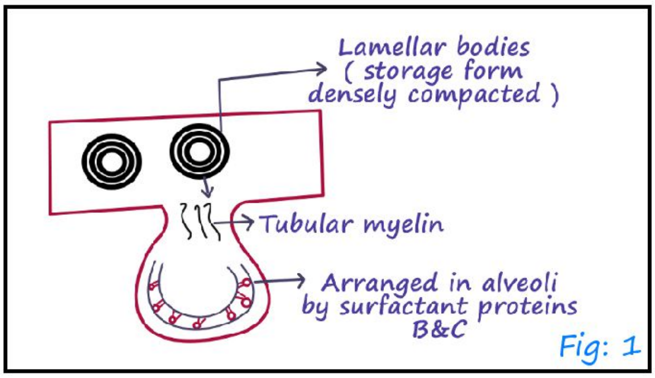
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MECHANICS OF BREATHING

Boyle's law:

$$PV = nRT \text{ (Constant)}$$

$$P \propto \frac{1}{V}$$

Intra alveolar pressure: (IAP) 00:01:10

Single alveoli-representing all alveoli in lung

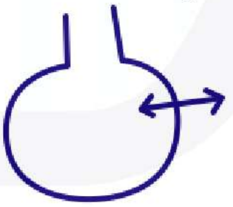


Fig: 1

- IAP at rest = 0 mm Hg (i.e. Equal to atmospheric pressure)
- IAP during inspiration ~ -1mmHg
- IAP at end of inspiration ~ 0mmHg
- IAP during expiration ~ +1mmHg
- IAP at end of expiration ~ 0 mmHg

Curve:

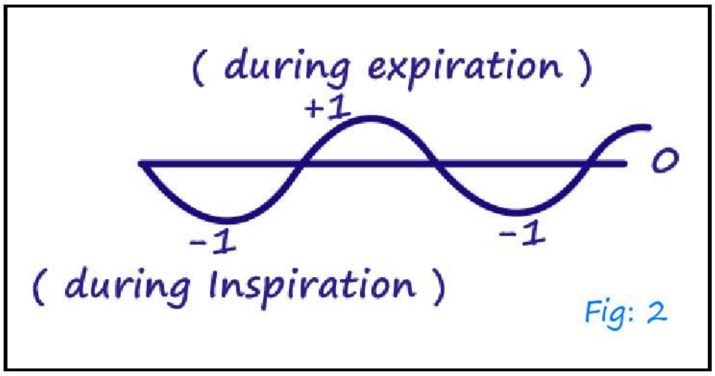


Fig: 2

- IAP is also called as intra pulmonary pressure

Intra pleural pressure (IPP) 00:05:00

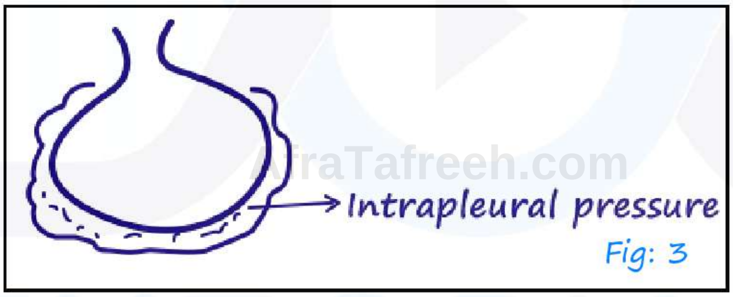


Fig: 3

- At rest = -2.5mm Hg = -3.4cm H2O
- Pressure conversion from mm Hg to Cm H2O

  Y mmHg = Y x 1.36cm H2O
- It is always negative except forceful expiration (Slightly positive)
- Intra pleural pressure is negative because

Opposite recoiling of
lung – Collapse
Thorax – Expand

Lymphatic drainage

Pneumothorax 00:09:30

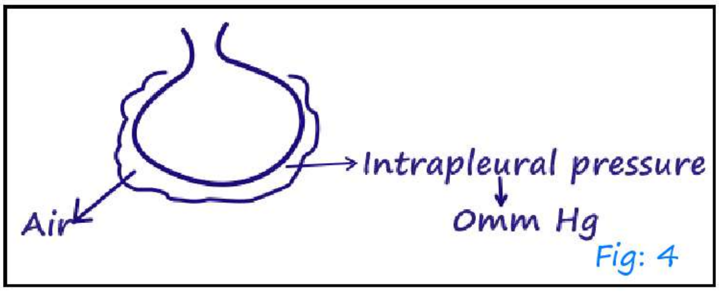


Fig: 4

- Pneumo – Air
- Thorax – in pleura
- In pneumothorax there is a breach in pleura
- As the tendency of the lung is to collapse in pneumothorax it will collapse
- Chest wall will expand
- Trachea/mediastinum shift to opposite side

Transpulmonary pressure 00:12:28

- IAP-IPP – = 0 – (–2) = + 2mm Hg

Respiratory muscles

Inspiration	Expiration
– Diaphragm (Main)	– Passive phenomenon due to lung recoiling
– Accessory	– During forced expiration
– external Intercostal muscle	o Rectus abdominis
– Scalene muscle	o Internal intercostal
– Sterno cleidomastoid muscle	o Transverse abdominis

Compliance and elasticity 00:16:00

Compliance	Elasticity
– It is the ease of expandability – $\Delta V/\Delta P$	– $\Delta P/\Delta V$

- Thick balloon – More elasticity
- Thin balloon – More compliance
- In emphysema – Decrease in elastance = Increase in elasticity

  Hyperinflation of lung
- In restrictive lung diseases – Compliance is decreased

  Eg : Interstitial lung disease – due to fibrosis
- Normal compliance of lung = Compliance of chest wall
- Which is 200ml/cm of H2O

  = 0.2 litre/cm of H2O
- Combined compliance of lung + Chest wall = 100ml/cm of H2O

  = 0.1 litre/cm of H2O

Dynamic compliance:

- It is during air flow

• At the start of inspiration • Alveoli – Small – Surface tension ↓ – Compliance ↑	• At the end of inspiration • Alveoli is – big – Surface tension ↑ – Compliance ↓

Specific compliance:

$$\frac{C}{FRC}$$

C – Compliance
FRC – Functional residual capacity

Compliance of lung:

- Even if the lung is collapsed there is certain amount of air inside it is called minimal volume i.e.; 10% of total lung capacity (TLC)
- Maximum amount of air in lung = TLC

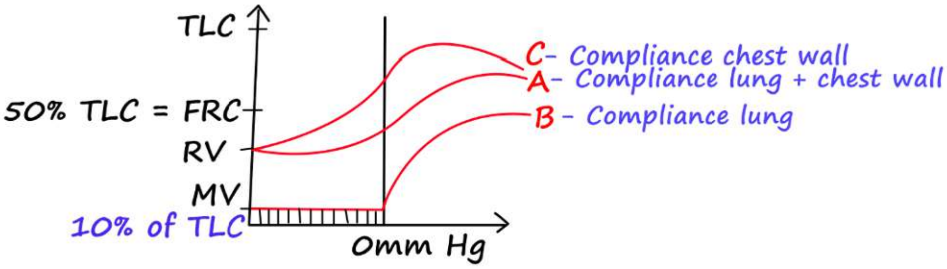
Compliance of thorax/chest wall

- At rest thorax expands 60% of TLC
- Maximum air = TLC
- Minimal = RV (Residual volume)

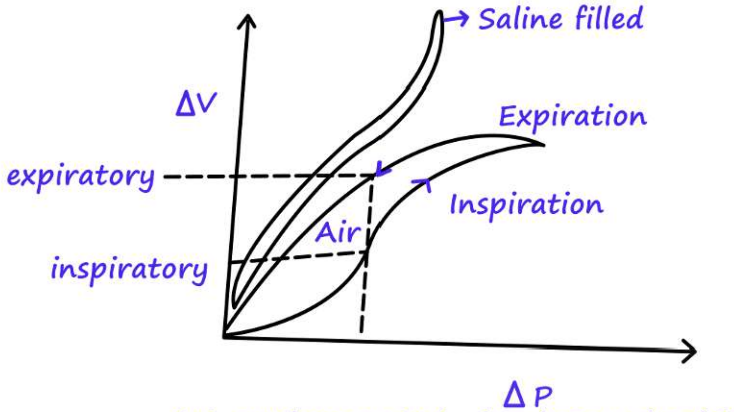
Compliance of lung + chest wall

- Maximum = TLC
- Minimum = RV

Curve of compliance:



Hysteresis 00:31:10



(V expiratory - V inspiratory) =ΔP

- During inspiration side heading
- Alveoli smaller,
- collapsing pressure more,
- surfactant decreases
- Therefore, volume is less
- During expiration side heading
- Alveoli larger
- collapsing pressure less
- surfactant more
- Therefore, volume is more

Cause of Hysteresis:

- Concentration of surfactant is different during expiration and inspiration.

  Hence the difference in volumes at same pressure

Work done by Lung – 0.5kg/min 00:36:00

- 65% Over come elasticity
  - 2/3 to overcome surface tension
  - 1/3 to overcome tissue elasticity
- 35% overcome the resistance
  - 25% airway resistance
  - 10% tissue resistance

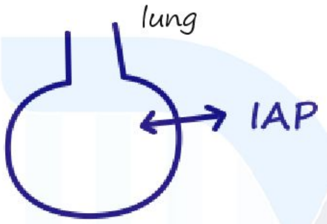
MECHANICS OF BREATHING

Boyle's law:

PV = nRT (Constant)

$$P \propto \frac{1}{V}$$

Intra alveolar pressure: (IAP) 00:01:10



Single alveoli-representing all alveoli in lung

Fig: 1

- IAP at rest = 0 mm Hg (i.e. Equal to atmospheric pressure)
- IAP during inspiration ~ -1mmHg
- IAP at end of inspiration ~ 0mmHg
- IAP during expiration ~ +1mmHg
- IAP at end of expiration ~ 0 mmHg

Curve:

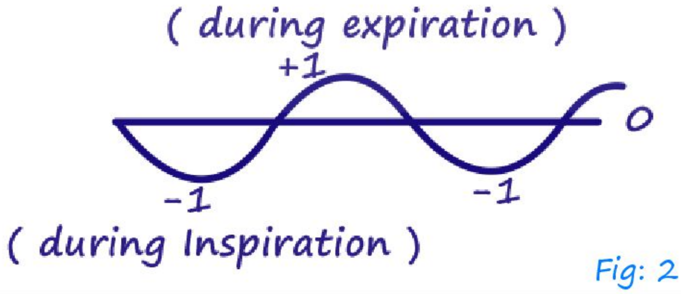


Fig: 2

- IAP is also called as intra pulmonary pressure

Intra pleural pressure (IPP) 00:05:00

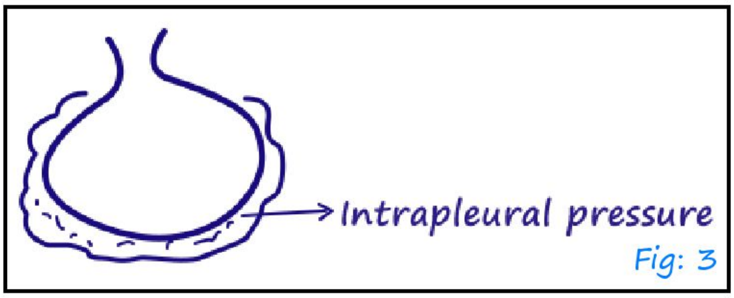


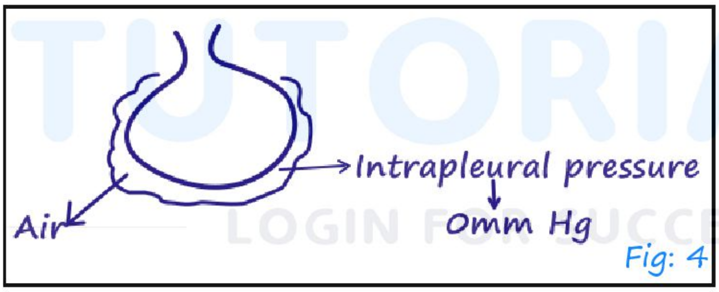
Fig: 3

- At rest = -2.5mm Hg = -3.4cm H2O
- Pressure conversion from mm Hg to Cm H2O

  Y mmHg = Y x 1.36cm H2O
- It is always negative except forceful expiration (Slightly positive)
- Intra pleural pressure is negative because

  - Opposite recoiling of lung – Collapse
    Thorax – Expand
  - Lymphatic drainage

Pneumothorax 00:09:30



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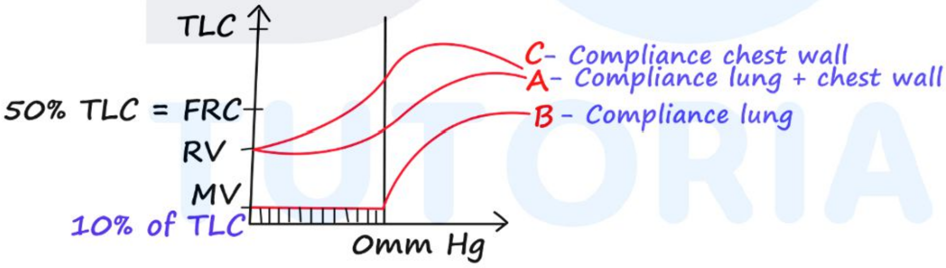

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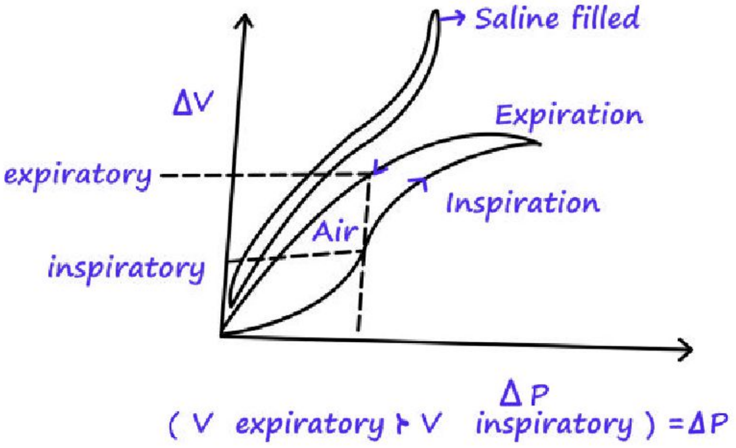

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ALVEOLAR VENTILATION AND PERFUSION

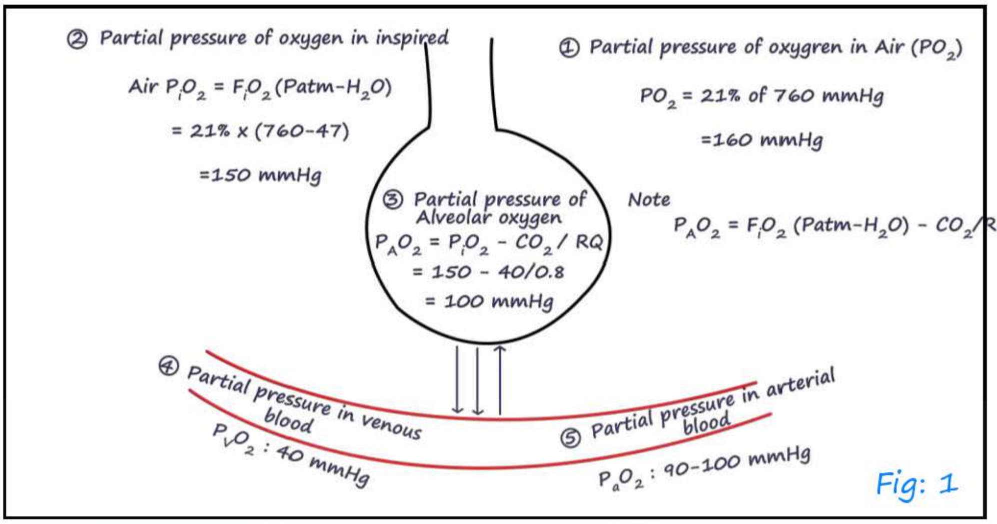
② Partial pressure of oxygen in inspired
Air $P_iO_2 = F_iO_2 (Patm-H_2O)$
$= 21\% \times (760-47)$
$=150$ mmHg
① Partial pressure of oxygren in Air (PO_2)
$PO_2 = 21\%$ of 760 mmHg
$=160$ mmHg
③ Partial pressure of Alveolar oxygen
$P_AO_2 = P_iO_2 - CO_2 / RQ$
$= 150 - 40/0.8$
$= 100$ mmHg
Note
$P_AO_2 = F_iO_2 (Patm-H_2O) - CO_2/RQ$
④ Partial pressure in venous blood
P_VO_2 : 40 mmHg
⑤ Partial pressure in arterial blood
P_aO_2 : 90-100 mmHg

Fig: 1

Pulmonary embolism 00:09:20

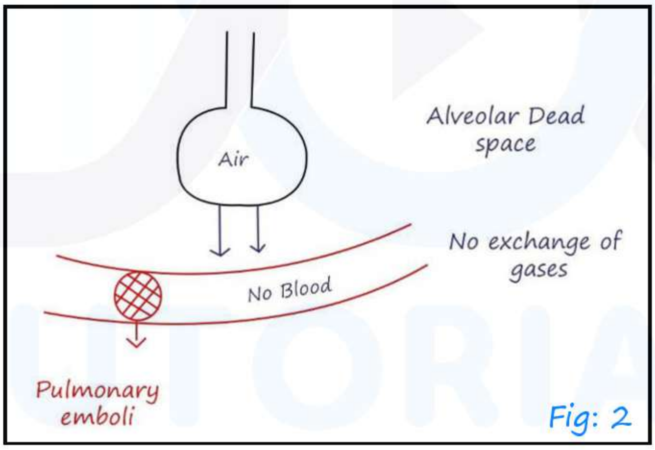
Air
Alveolar Dead space
No exchange of gases
No Blood
Pulmonary emboli

Fig: 2

- V/Q = Air/Perfusion = Air/0 = ∞
- $PA\ O2 = PiO2 = 150$mmHg

Airway obstruction 00:13:02

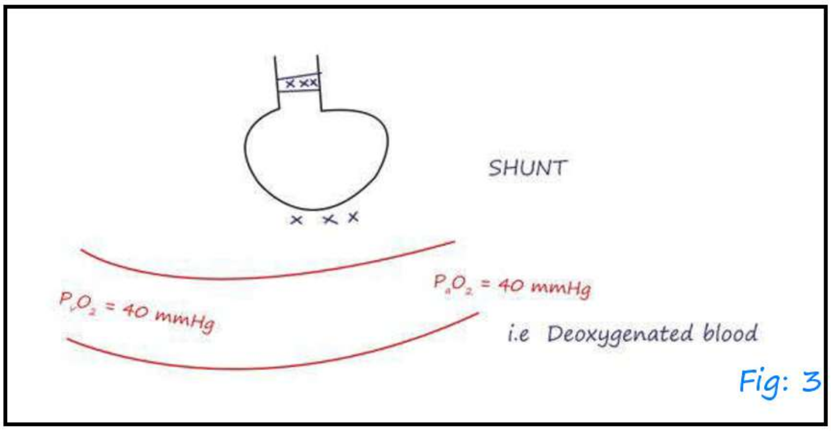
SHUNT
$P_aO_2 = 40$ mmHg
$P_vO_2 = 40$ mmHg
i.e Deoxygenated blood

Fig: 3

- Pa O2 = PV O2 = 40mmHg

$$\frac{V}{Q} = \frac{0}{\text{Perfusion}} = 0$$

Physiological dead space:

= Anatomical dead space + Alveolar dead space

- A/K/A – Total dead space
- Normally
  - Alveolar dead space = 0
  - Therefore, physiological dead space = Anatomical dead space
- Pathological
  - Alveolar dead space present
  - Therefore, physiological dead space > Anatomical dead space
  - Dead space = 2 x wt (kg) or wt in pound

TUTORIALS LOGIN FOR SUCCESS

$$VD = VT \times \frac{PACO2 - PeCo2}{PACo2}$$

- VD – Volume of Dead space
- PaCo2 – Co2 in Alveolar air
- PeCo2 – Co2 in expired air

- Minute ventilation – Tidal Volume (TV) x RR
- Alveolar ventilation = (TV – Dead space) x RR

V/Q ratio 00:24:50

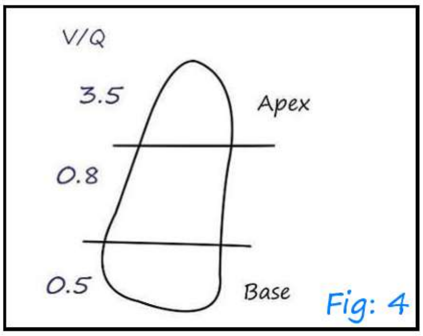

Fig: 4

- V max (Maximum ventilation) is at Base i.e., due to smaller alveoli & more compliance
- Q max (perfusion maximum) is at base
- V/Q maximum at apex: perfusion is very less than ventilation

Pulmonary circulation 00:27:30

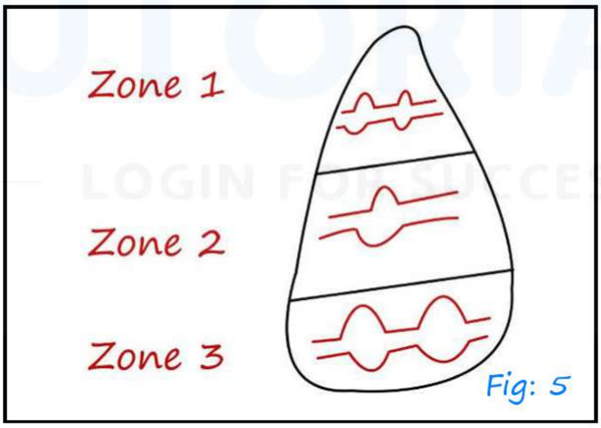

Fig: 5

- Pulmonary artery = Deoxygenated blood
- Pulmonary vein = Oxygenated blood
- Pulmonary capillary = Oxygenated blood
- Zones 1: $P_A > P_a > P_V$ = No blood

- Zones 2: $P_A > P_a > P_V$ = Intermittent blood (Water fall effect)
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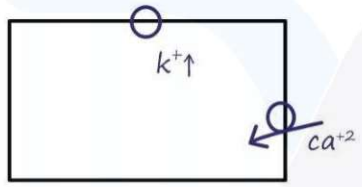
Hypoxia

- Always vasodilation – In systemic circulation
- Vasoconstriction – Pulmonary circulation
- Due to O2 sensitive K^+ channel S



In Hypoxia k^+ retention

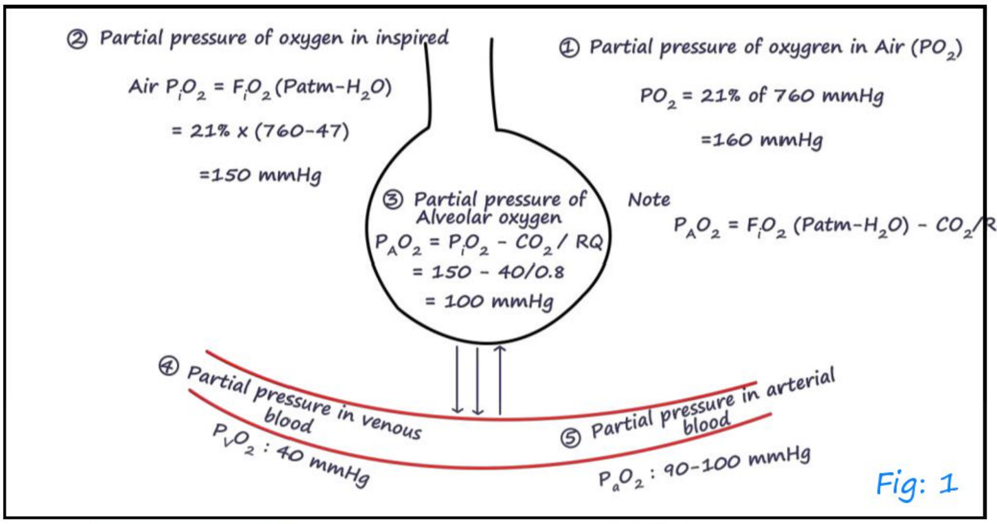
↓

Depolarization & ca^{+2} influx occur

↓

Vasoconstriction

ALVEOLAR VENTILATION AND PERFUSION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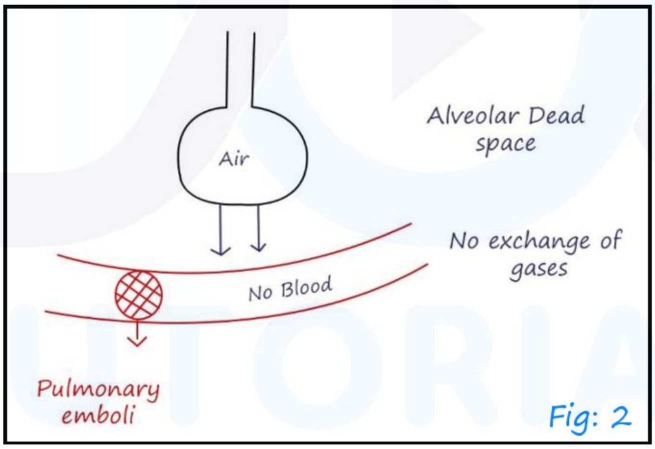
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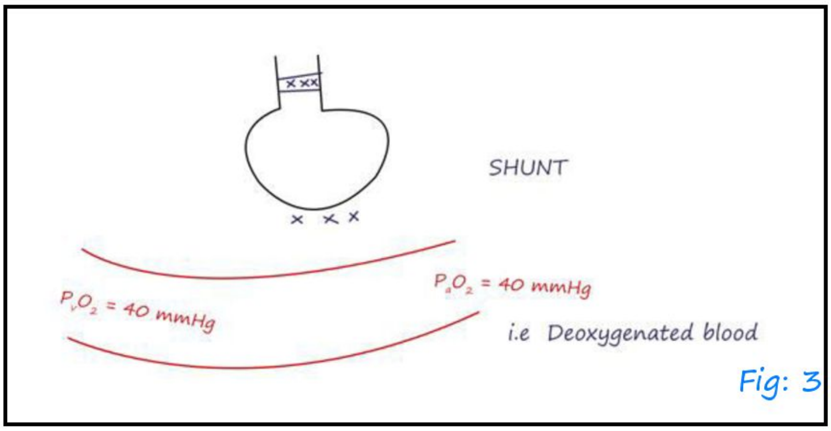
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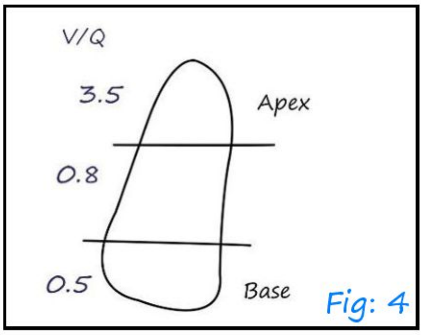
V/Q ratio 00:24:50



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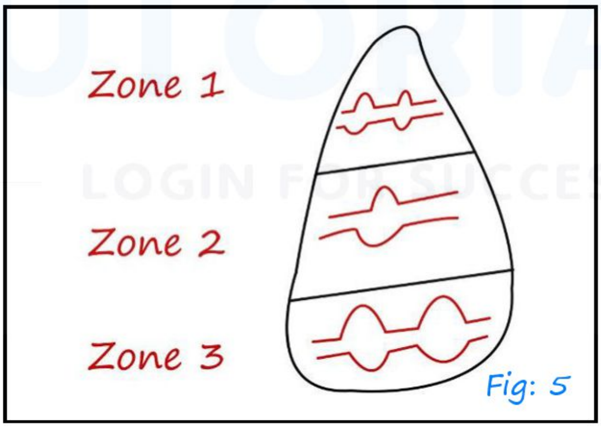
Pulmonary circulation 00:27:30

TUTORIALS LOGIN FOR SUCCESS



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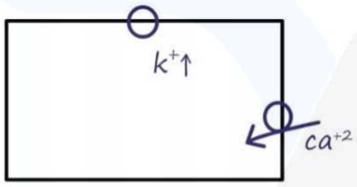

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Depolarization & ca^{+2} influx occur

↓

Vasoconstriction

LUNG VOLUMES AND CAPACITY

Lung volumes and capacity

Static
↓
Spirometry

Dynamic – Time factor is involved
↓
Flow volume loop curve

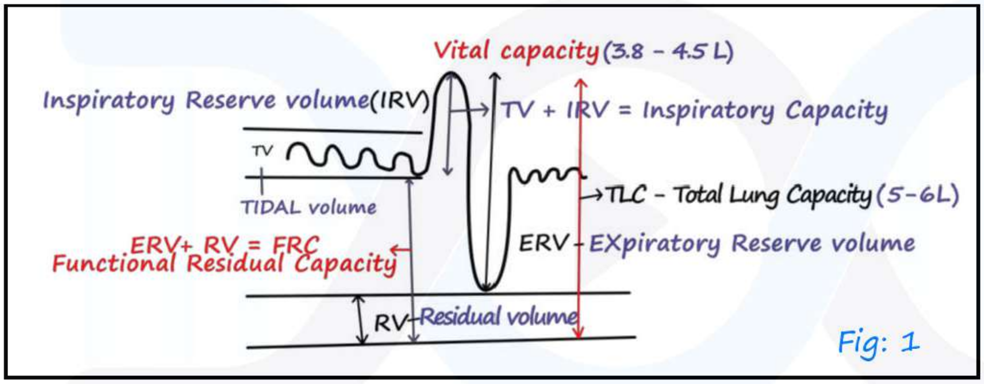
Vital capacity (3.8 – 4.5 L)
Inspiratory Reserve volume(IRV)
TV + IRV = Inspiratory Capacity
TV
TIDAL volume
TLC – Total Lung Capacity (5–6L)
ERV+ RV = FRC
Functional Residual Capacity
ERV
EXpiratory Reserve volume
RV
Residual volume

Fig: 1

- TV: amount of air inspired and expired normally at rest 500ml (Approx)
- IRV: Air inspired above & over TV (2–3L)
- ERV: Air expired above & over TV – 1.3L
- RV: Amount of air left in lung even after forceful expiration (1.2L)
- Total lung capacity: It depends on compliance of lung
- Closing volume: Lung volume above residual volume at which airways in lower dependent portion of lung – Begin to close
- CV = 10% x VC
- It ↑ with age up to 40% VC

Spirometry cannot measure

- Residual volume
- FRC (ERV + RV)
- TLC (VC + RV)

Methods to measure FRC

- Also known as equilibrium volume

i. Helium dilution method

- $$\text{FRC} = \underset{\substack{\downarrow \\ \text{Initial volume}}}{V} \times \frac{C1 - C2}{C_2}$$

C1 = Initial concentration of helium
C2 = Final concentration of helium

ii. Nitrogen washout method

- FRC = V x C1/C2
- C1 = Initial concentration of N1
- C2 = Final concentration of N2

iii. Body plethysmography

- P1 V1 = P2 V2
- Most common clinical method used

AfroTafreeh.com
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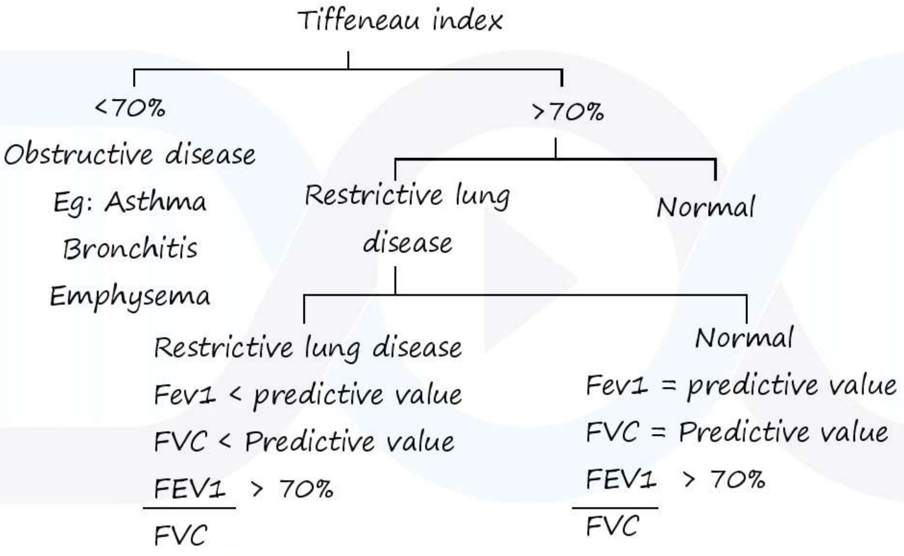
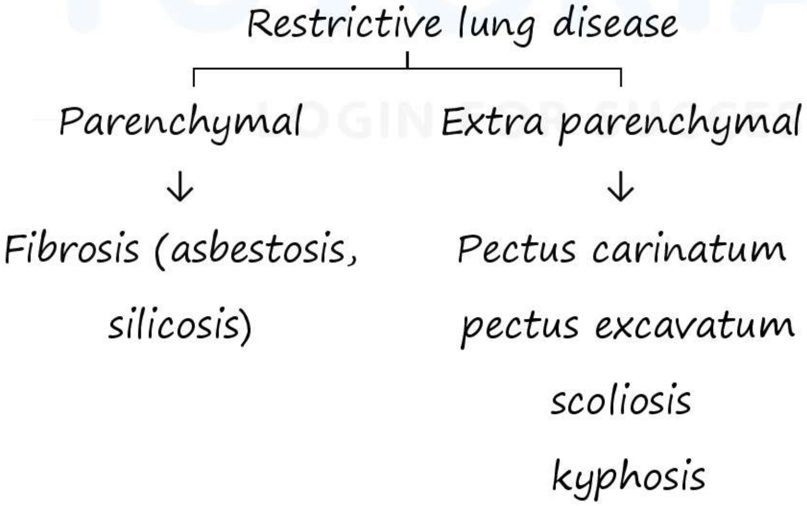
Dynamic lung volume and capacity 00:15:00

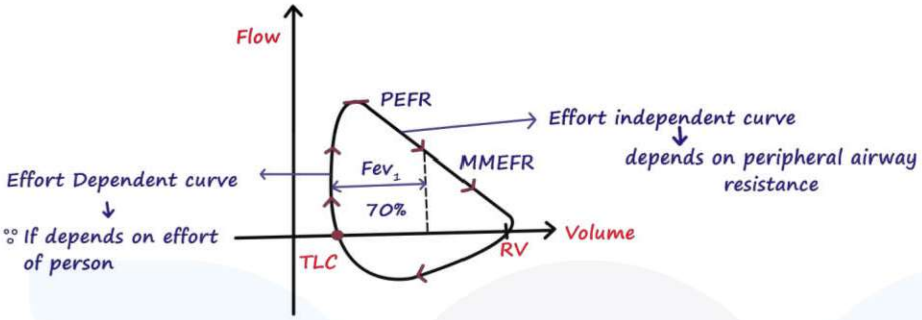
- Fev1 - Air expired in 1sec forcefully after taking full inspiration
- FVC – Max air expired forcefully after taking full inspiration
- Fev1/FVC

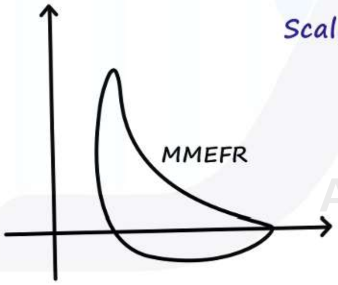

Tiffeneau index
<70%
Obstructive disease
Eg: Asthma
Bronchitis
Emphysema
>70%
Restrictive lung disease
Normal
Restrictive lung disease
Fev1 < predictive value
FVC < Predictive value
FEV1/FVC > 70%
Normal
Fev1 = predictive value
FVC = Predictive value
FEV1/FVC > 70%


Restrictive lung disease
Parenchymal
Fibrosis (asbestosis, silicosis)
Extra parenchymal
Pectus carinatum
pectus excavatum
scoliosis
kyphosis

- PEFR – Peak expiratory flow rate it is maximum airflow during forceful expiration

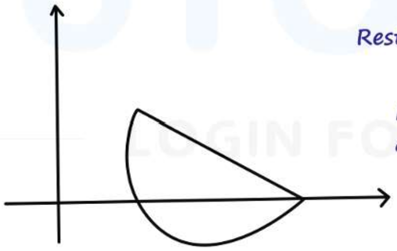
- MMEFR – Maximum mid expiratory flow rate
  it is the first parameter to decrease in small airway obstruction


Flow
PEFR
Effort independent curve
↓
depends on peripheral airway resistance
MMEFR
Fev$_1$
70%
Effort Dependent curve
↓
∵ If depends on effort of person
Volume
TLC
RV

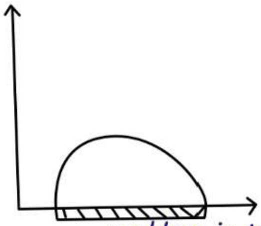


Scalloped curve / Dog leg pattern
↓
Seen in obstructive lung Disease

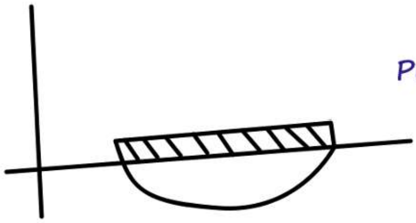
TUTORIALS
LOGIN FOR ACCESS



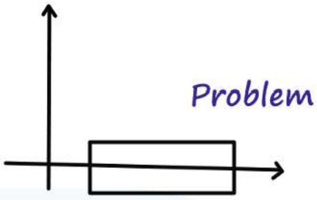
Restrictive Lung Disease
↓
Normal shape but with decreased volumes.



problem in Inspiration
↓
Extrathoracic Obstruction



Problem in expiration
↓
Intrathoracic obstruction



Problem in both inspiration & Expiration
Box Shaped curve
eg : Foreign body

Lung disease

Obstructive	Restrictive
- Trapping of Air ↓ Leading to increase in RV & TLC	Diffusion decreased
- $FEV_1/FVC < 70\%$	- $FEV_1/FV > 70\%$
- DLCO: Decreased in Emphysema	- DLCO decreased
- Compliance increases	- Compliance decreases

Note

- VC decreases in both lung diseases

LUNG VOLUMES AND CAPACITY

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↓
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Dynamic – Time factor is involved
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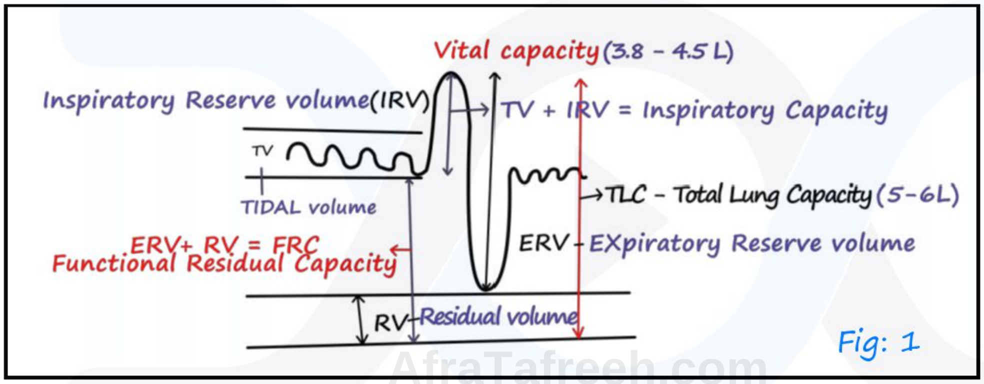
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AfraTafreeh.com

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- IRV: Air inspired above & over TV (2–3L)
- ERV: Air expired above & over TV – 1.3L
- RV: Amount of air left in lung even after forceful expiration (1.2L)
- Total lung capacity: It depends on compliance of lung
- Closing volume: Lung volume above residual volume at which airways in lower dependent portion of lung – Begin to close
- CV = 10% x VC
- It ↑ with age up to 40% VC

TUTORIALS LOGIN FOR SUCCESS

Spirometry cannot measure

- Residual volume
- FRC (ERV + RV)
- TLC (VC + RV)

Methods to measure FRC

- Also known as equilibrium volume

i. Helium dilution method

$$\text{FRC} = \underbrace{V}_{\text{Initial volume}} \times \frac{C1 - C2}{C_2}$$

C1 = Initial concentration of helium

C2 = Final concentration of helium

ii. Nitrogen washout method

- FRC = V x C1/C2
- C1 = Initial concentration of N1
- C2 = Final concentration of N2

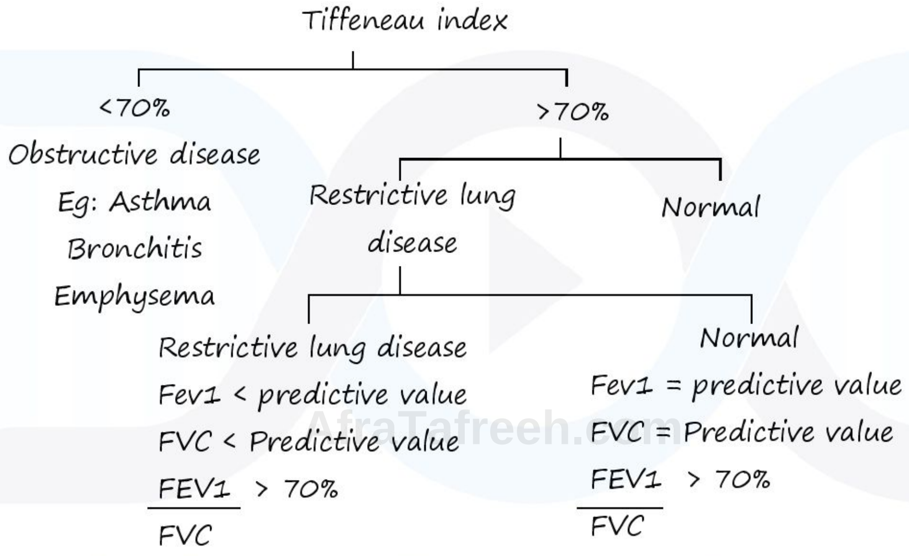
iii. Body plethysmography

- P1 V1 = P2 V2
- Most common clinical method used

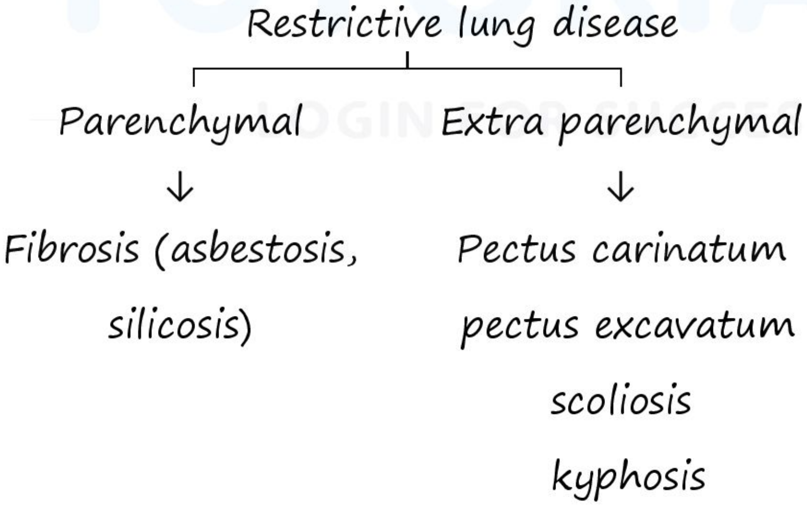
TUTORIALS LOGIN FOR SUCCESS

Dynamic lung volume and capacity 00:15:00

- Fev1 - Air expired in 1sec forcefully after taking full inspiration
- FVC – Max air expired forcefully after taking full inspiration
- Fev1/FVC

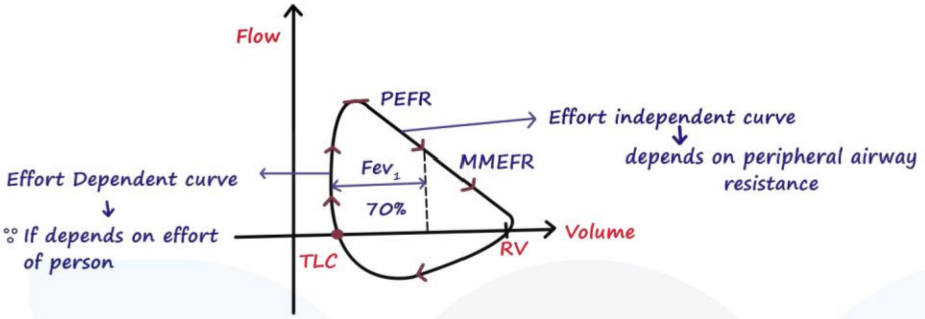

Tiffeneau index
<70%
Obstructive disease
Eg: Asthma
Bronchitis
Emphysema
>70%
Restrictive lung disease
Normal
Restrictive lung disease
Fev1 < predictive value
FVC < Predictive value
FEV1/FVC > 70%
Normal
Fev1 = predictive value
FVC = Predictive value
FEV1/FVC > 70%

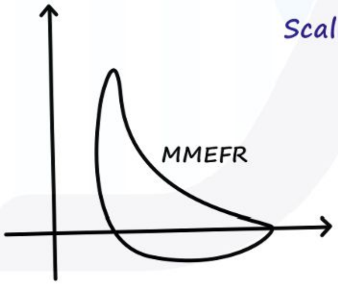
TUTORIALS LOGIN FOR SUCCESS


Restrictive lung disease
Parenchymal
Fibrosis (asbestosis, silicosis)
Extra parenchymal
Pectus carinatum
pectus excavatum
scoliosis
kyphosis

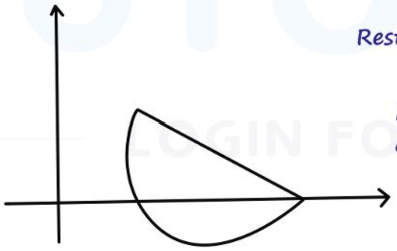
- PEFR – Peak expiratory flow rate it is maximum airflow during forceful expiration

- MMEFR – Maximum mid expiratory flow rate
  it is the first parameter to decrease in small airway obstruction

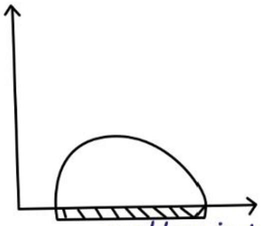

Flow
PEFR
Effort independent curve
↓
depends on peripheral airway resistance
MMEFR
Fev$_1$
70%
Effort Dependent curve
↓
∵ If depends on effort of person
Volume
TLC
RV



Scalloped curve / Dog leg pattern
↓
Seen in obstructive lung Disease

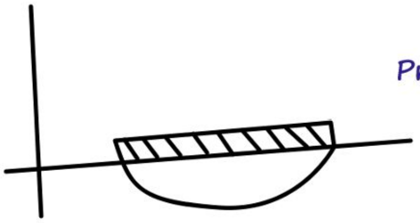


Restrictive Lung Disease
↓
Normal shape but with decreased volumes.

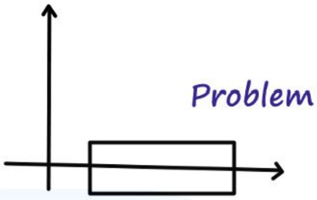


problem in Inspiration
↓
Extrathoracic Obstruction

TUTORIALS
LOGIN FOR ACCESS



Problem in expiration
↓
Intrathoracic obstruction



Problem in both inspiration & Expiration
Box Shaped curve
eg : Foreign body

Lung disease

Obstructive	Restrictive
- Trapping of Air ↓ Leading to increase in RV & TLC	Diffusion decreased
- $FEV_1/FVC < 70\%$	- $FEV_1/FV > 70\%$
- DLCO: Decreased in Emphysema	- DLCO decreased
- Compliance increases	- Compliance decreases

Note

- VC decreases in both lung diseases

TRANSPORT OF GASES

Diffusion and transport of gases

- Fick's law of diffusion

  $$V = \frac{\Delta P \times A \times D}{t}$$

  ΔP: – Pressure difference

  A: – Surface area

  D: – Diffusion coefficient $= \frac{\text{Solubility}}{\sqrt{\text{Molecular wt}}}$

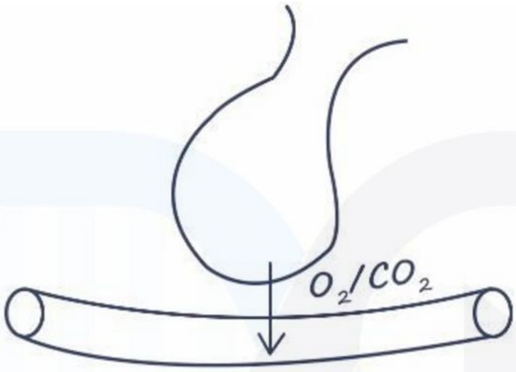
  T: – Thickness
- First inner most layer – fluid + surfactant
- Alveolar epithelium larger
- Epithelial basement membrane
- Interstitial layer
- Capillary BM
- Capillary endothelium
- Alveolar capillary membrane: – 0.2 to 0.5 μ
- In emphysema → trypsin activity will destroy membrane

  – Decrease surface area

  – Diffusion decrease
- In all other restrictive lung disease, there is fibrosis of lung parenchyma, which will decrease the rate of diffusion → thickness is more
- DLCO

  – 2.5 ml/min/mmHg

- Decreased in emphysema
  Pulmonary fibrosis
  Anemia
- Increased in exercise / polycythemia
- 2 types of gases
  1. Diffusion limited gas → CO



2. Perfusion limited gas → N_2O, O_2, CO_2

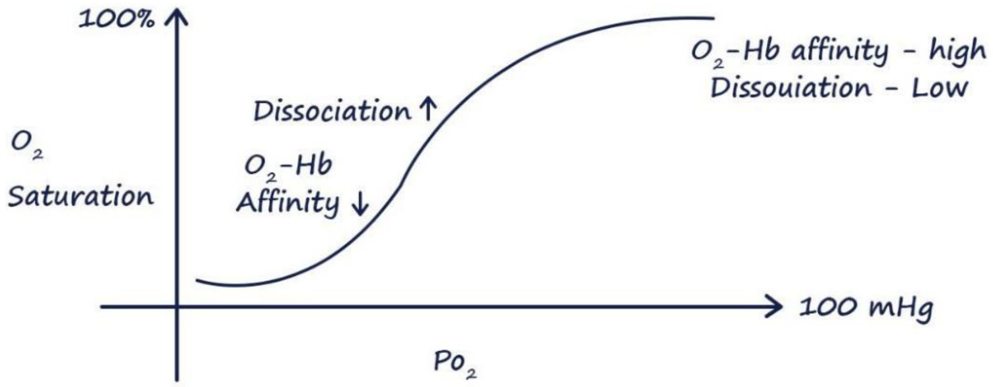
- If you increase perfusion, plasma will increase, diffusion also
- More the diffusion, more the perfusion
- Co tightly binds with Hb of RBC

Transport of gases 00:09:19

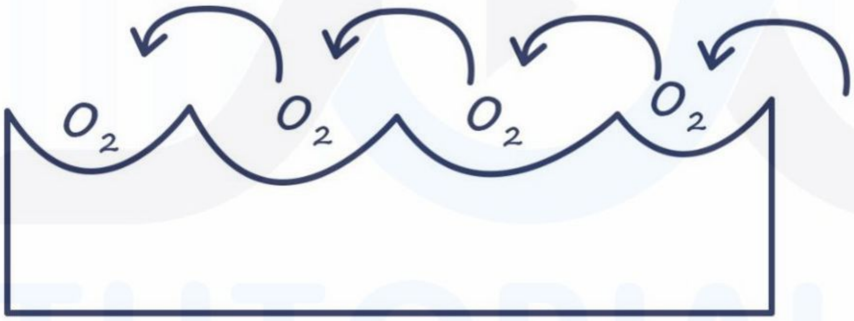
Transport of O_2

Dissolved form 3%	Combined with Hb 97%
1 mmHg Po_2	0.003 mlO_2 / 100ml blood
100 mmHg	0.3 ml O_2 / 100mL
1 gm Hb	1.34 ml O_2 / 100 ml
15 gr Hb	1.34 x 15 ~ 21 ml O_2 / 100 ml

Hb carries O_2 70 times than ....?



- O_2 – dissociation curve is sigmoid in nature
- Cooperative binding
- 4 O_2 molecule attaches with Hb

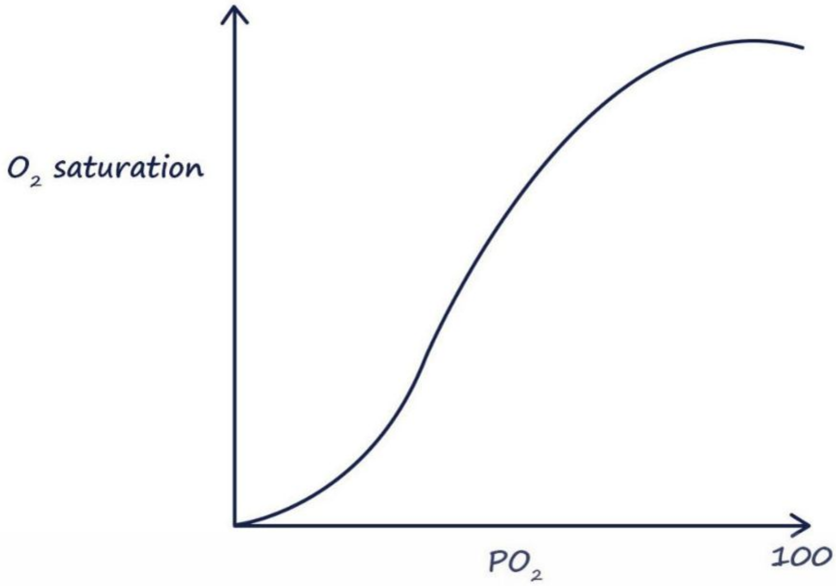


- Binding of one O_2 molecule with Hb attract second O_2 molecule similarly 3rd and 4th O_2 molecule

Hb

Tight
↓
When Hb is in tight position, it does not favouor binding
↓
Dissociation of O_2 will be more, affinity is low

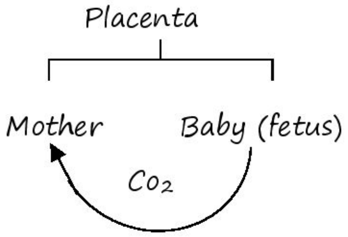
Relax
↓
Favours O_2 binding (Dissociation of O_2 decrease, affinity of Hb- O_2 increase



<table>
<tr><th>Right
↓</th><th>left
↓</th></tr>
<tr><td>• Affinity of Hb-O_2 decrease
• Dissociation increase
↓
• Acidosis (↓pH / ↑Co_2
• Increase temperature
• Increase 2, 3 DPG
• Exercise
• High altitude</td><td>• Affinity increase
• Dissociation decrease
↓
• Alkalosis (↑pH / ↓Co_2
• Decrease temperature
• Fetal Hb
- High affinity to O_2
- Less affinity to 2,3 DPG
• Meth-Hb
• Stored blood → decrease 2,3 DPG</td></tr>
<tr><td colspan="2">In chronic acidosis → inhibit glycolytic enzyme decrease 2, 3 DPG no effect on curve</td></tr>
</table>

- Bohr effect → Decrease in affinity to Hb when pH decrease / Co_2 increase

Double Bohr effect



- CO_2 goes from baby to mother, feotus becomes alkaline, mother becomes acidic

↓

Left shift in foetus

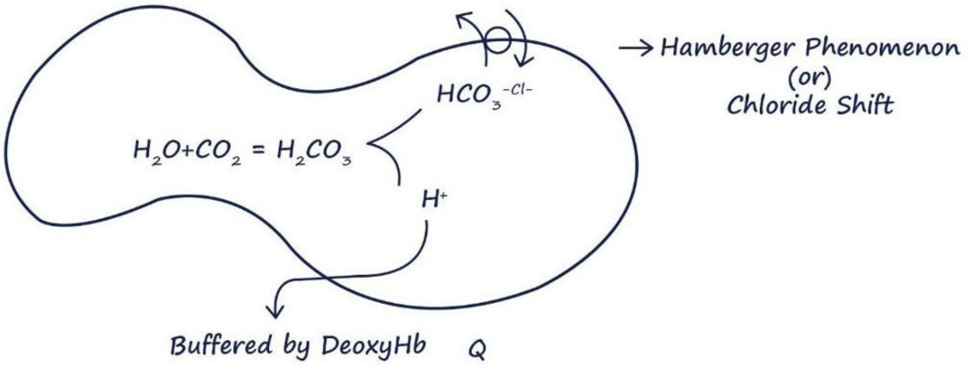
Right shift in mother

- P50 – partial pressure of O_2 at which Hb is 5% saturated – 27 mmHg
  - Lower is p50 – higher is affinity / lesser will be O_2 dissociation
  - Acidosis – inhibit glycolysis

    ↓ 2, 3 DPG
- $Hb + O_2 + 2,3\ DPG \rightarrow Hb - 2,3\ DPG + O_2$
- In stored blood, 2, 3 DPG decrease, O_2 release less
  - ACD → Acid citrate dextrose
  - CPDA → Citrate phosphate dextrose adenin
    - Increase 2,3 DPG / increase, O_2 release
    - Increase p50 / Right shift

Transport of CO_2

- Dissolved form 7%
- Combined Hb 23%
- (in form of) HCO_3^-


HCO_3^- Cl^-
$H_2O+CO_2 = H_2CO_3$
H^+
Buffered by DeoxyHb
Q
→ Hamberger Phenomenon
(or)
Chloride Shift

- PCV is 3% higher in venous blood

↓

Chloride influx

↓

H_2O into cell → cell swells increase packed cell volume

Q. The oxygen carrying capacity of a 18 year old boy with haemoglobin of 14g/dl is

A. 18 ✓
B. 16
C. 14
D. 22

TUTORIALS
LOGIC FOR SUCCESS

Q. Decrease in pH shifts the oxygen dissociation curve to

A. Left
B. Does not affect
C. On either side depending on other factors
D. Right ✓

Q. The fact that packed cell volume (PCV) is raised in venous blood can be explained by means of

A. Chloride shits ✓
B. Haldane effect
C. Bohr effect
D. Affinity of Hb to 2,3-DPG

NEURAL CONTROL OF RESPIRATION

Regulation of respiration

Bohr Effect

- O_2 – Hb dissociation curve shifts to right in cases of Acidosis

Haldane Effect

- O_2 binds with Hb (Hemoglobin)
- CO_2 released

Regulation of respiration 00:01:21

Neural Control

Voluntary Control
↓
Centre is in limbic cortex

Involuntary Control
↓
Centre is in brain stem

Medulla
↓
Rhythm of the respiration generated

Pons
↓
Fine tuning of respiration

DOI TUTORIALS LOGIN FOR SUCCESS

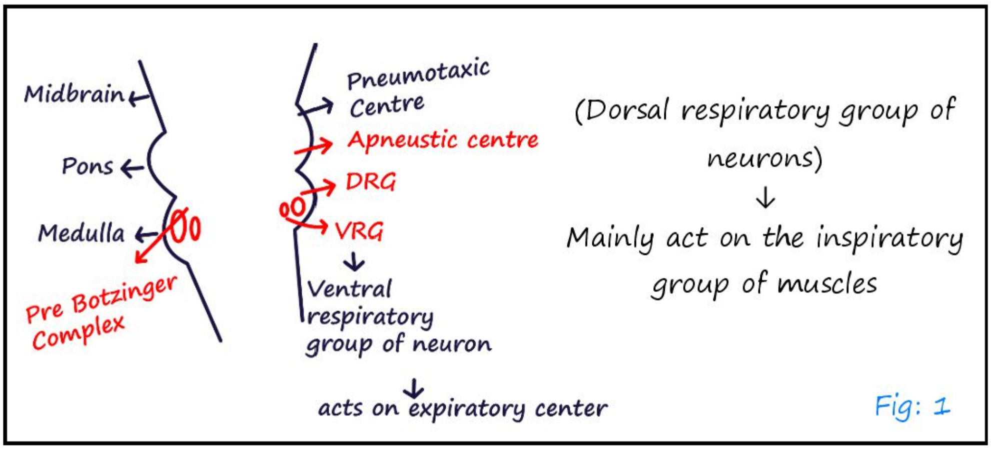
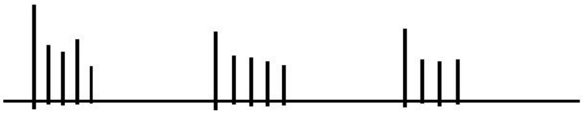

Midbrain
Pons
Medulla
Pre Botzinger Complex
Pneumotaxic Centre
Apneustic centre
DRG
VRG
Ventral respiratory group of neuron
acts on expiratory center
(Dorsal respiratory group of neurons)
Mainly act on the inspiratory group of muscles

Fig: 1

- Pacemaker is pre-Botzinger complex (PBC) → Gives RAMP signal to DRG



- Apneustic center is in Lower Pons → Also stimulates the DRG
- Pneumotaxic centre → inhibits DRG

Medulla → DRG → Inspiration

VRG → Expiration (during exercise)

Pacemaker is the **Pre-Botzinger complex** which gives out RAMP Signals

Apneustic centre → Stimulate DRG → Continues the inflation of lungs

Break → **Pneumotaxic centre** → Inhibits the DRG

Accelerator

Vagus nerve along with Pneumotaxic centre stops respiration

↓↓

Prevent overinflation of the lungs

- Pneumotaxic centre limits respiration by inhibiting apneustic centre → Increases the Respiratory rate
- Apneustic centre → Prolongs inspiration
- VRG has no role in controlling expiration except during forceful expiration and exercise
- Extra respiratory effort during exercise is called as **extra-respiratory drive or over-drive phenomenon**

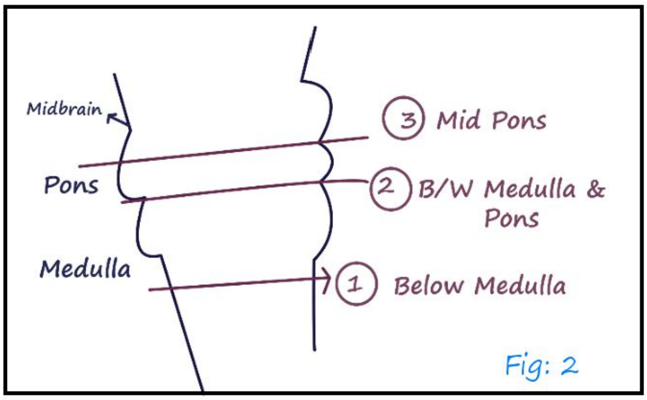

Midbrain
Pons
Medulla
③ Mid Pons
② B/W Medulla & Pons
① Below Medulla

Fig: 2

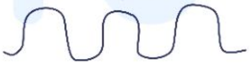
- If lesion is below the medulla → Respiration will stop
- If lesion between medulla and pons → Respiration will be irregular
- Mid pontine lesion → between apneustic centre and Pneumotaxic centre

↓↓

Prolonged inspiration

If Vagus nerve intact

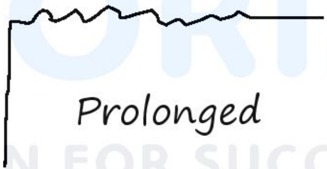
↓



Deep & Slow respiration

Vagus nerve cut

↓



Prolonged inspiration

↓

Apneusis

- **Herring – Breuer Inflation Reflex →** Overinflation of the lung inhibits further inflation → Vagus nerve
- **Herring – Breuer Deflation Reflex →** Deflation of the lung increases respiratory rate

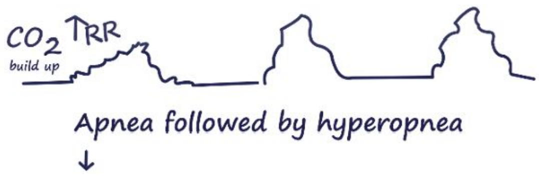
- **Paradoxical Reflex of Head →** First cry of newborn → Inflation causes further inflation

J Receptor/reflex

- J stands for Juxta pulmonary capillary
- Reflex was discovered by Dr. A.S. Paintal
- Endings of slow conducting unmyelinated
- Activated by
    - Pulmonary congestion
    - Increase in interstitial fluid
    - Hyperinflation of the lung
    - Intravenous injection of Capsaicin
- Responses
    - BP will be low → Hypotension
    - Bradycardia (HR decrease)
    - Apnea → followed by increased RR

Altered breathing pattern 00:28:50

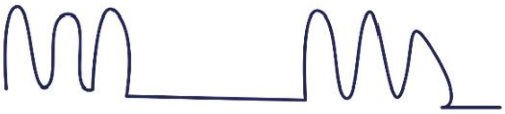
i. Cheyne–Stokes breathing



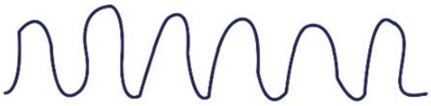
CO_2 build up → gradual increase in RR followed by gradual decrease in RR

ii. Biot's Breathing

Regular deep inspiration followed by apnea

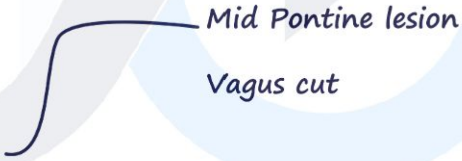


iii. Kussmaul's breathing – Air hunger



Increased depth & prolonged inspiration → CO_2 washed out

iv. Apneustic prolonged inspiration


Mid Pontine lesion
Vagus cut

CHEMICAL CONTROL OF RESPIRATION

Peripheral Chemoreceptors 00:00:30

Peripheral chemoreceptor

Carotid body

Aortic body

Glomus cell → O_2 sensitive K^+ channel

↓

Increased respiratory rate causing a CO_2 washout

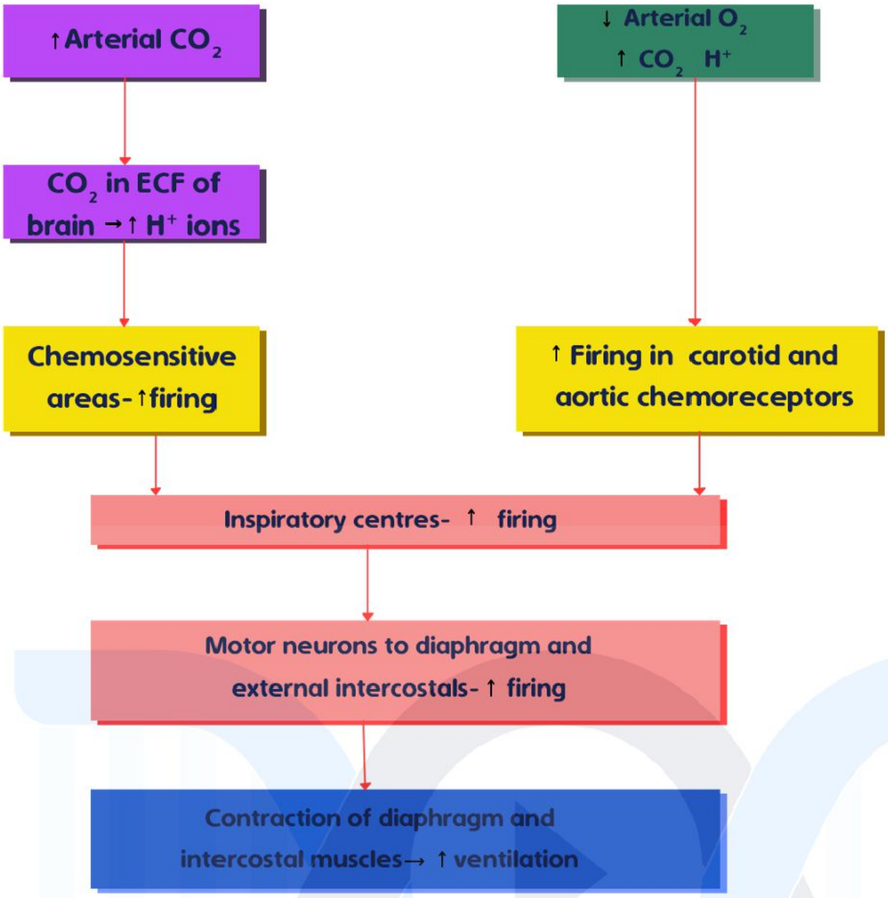
Stimulus

- Decreased pO_2 (Hypoxia)
- Increase CO_2
- Increase H^+ ions

DOC TUTORIALS
LOGIN FOR SUCCESS

Central chemoreceptor 00:04:33

- Also known as Medullary Chemoreceptors
  - Direct stimulator → H^+ ions
  - Increased pCO_2 → (Hypercapnea)


↑Arterial CO_2
CO_2 in ECF of brain →↑ H^+ ions
Chemosensitive areas-↑firing
↓ Arterial O_2
↑ CO_2 H^+
↑ Firing in carotid and aortic chemoreceptors
Inspiratory centres- ↑ firing
Motor neurons to diaphragm and external intercostals- ↑ firing
Contraction of diaphragm and intercostal muscles→ ↑ ventilation

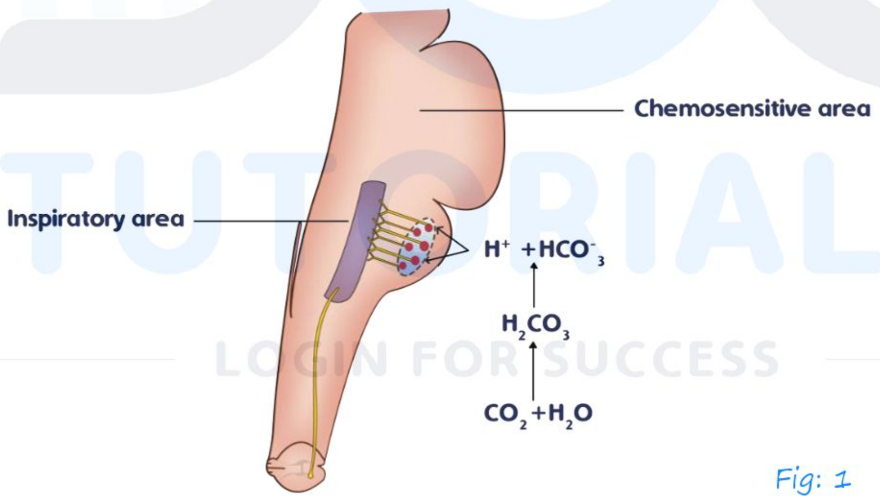

Chemosensitive area
Inspiratory area
$H^+ + HCO_3^-$
H_2CO_3
$CO_2 + H_2O$

Fig: 1

Increase in CO_2 → CCR Stimulated → Increased RR

Decrease in CO_2 → CCR Inhibited → Decreased RR

Hypoxia 00:07:17

1.Hypoxic hypoxia

Decrease pO_2 (Dissolved form) Ex. High altitude or other causes

↓

Activates Peripheral CR such as Glomus Cells

↓

Increased RR

Management: O_2 supplementation

2.Anemic hypoxia

- Anemia/CO poisoning
- Decreased RBC → Decreases Hb → Decreased O_2 concentration in the blood
- Peripheral chemoreceptors are not activated because they respond to pO_2 not Hemoglobin

3.Stagnant hypoxia/Ischemic hypoxia

- Decreased CO / Ischemia
- Arteriovenous O_2 difference increases
- Cyanosis can be seen in Stagnant Hypoxia

4.Histotoxic hypoxia

- In Cyanide poisoning – Affects Cytochrome Oxidase
- Arteriovenous O_2 difference decreases
- Defect in O_2 utilization → Peripheral chemoreceptors are maximally stimulated.

ENVIRONMENTAL PHYSIOLOGY

Deep Sea Physiology 00:00:05

- At sea level, we have atmospheric pressure (1 atm)
- As you move deep, for every 10m, 1 atm increase

↓

Causes compression of the gases

↓

On sudden decrease of pressure – Bubbles

↓

Decompression sickness aka Caisson's disease/Dysbarism

Symptoms

- Bubble can enter into tissue/muscle/tendon/joint leading to Pain → Bends
- Dyspnea → Chokes
- Most common cause of death → Air Embolism
- **Treatment:** Put the person in a hyperbaric chamber → Increase the pressure and decrease the pressure slowly later on
- **Nitrogen narcosis:** Nitrogen dissolves in body fluids if we work for longer periods of time
- Nitrogen (High affinity for lipids)

  ↓

  Dissolves in the neuronal membrane of myelin

  ↓

  Nitrogen narcosis
- Similar to alcohol intoxication → Loss of recent memory, Fine motor activity can also be impaired

Space 00:06:52

- When you are going towards the earth

  ↓

  Distance is decreasing

  ↓

  Positive G
- When you are going away in the space

  ↓

  Influence of gravity decrease

  ↓

  Distance is increasing

  ↓

  Negative G
- If you are going towards earth (+g)

  ↓

  Gravity will act from head to toe

  ↓

  Decreased cardiac output

  Decreased supply to the brain

  ↓

  Black out/grey out
- If you are going away from gravity (-g)

  ↓

  Blood goes from foot to head

  ↓

  Eyes & brain get congested

  ↓

  Red out
- Zero gravity
  - Bone mass decreases
  - Muscle mass decreases

TUTORIALS LOGIN FOR SUCCESS

- Work capacity also decreases

Mountain sickness 00:10:19

- High altitude → decreases pO2 → Hypoxia

↓

Peripheral chemoreceptors are activated

↓

Increased RR

↓

CO_2 wash out

↓

Compensatory met. alkalosis ← Respiratory alkalosis

↓

Decreases free calcium → Tetany

- Hypoxia is the most potent stimulus for EPO
- Release of VEGF → increases angiogenesis
- Increase in the diffusion of Gases and also DLCO
- Increase O_2 utilization at the level of cell by increasing mitochondrial enzyme activity

TUTORIALS LOGIN FOR SUCCESS

Acute mountain sickness

- Occurs within 6-12 hours of Ascent
- Clinical features
  - Nausea
  - Vomiting
  - Headache
  - Insomnia

- Descent to lower altitudes is the best possible treatment
- If severe → It affects your lung → Lung edema

↓

HAPE

(High altitude pulmonary edema)

↓

- Brain edema → HACE (High altitude cerebral edema)
- Oxygen Support is to be given
- Calcium blockers like nifedipine and other drugs like Dexamethasone and Acetazolamide

Chronic mountain Sickness

- Pulmonary hypotension
- Treatment: Acetazolamide → Releases of Bicarbonates → Leads to Metabolic Acidosis → Respiratory alkalosis → Hyperventilation

GLOMERULUS

Kidneys

↓

- Excretion
- Endocrine function (Rennin)
- Homeostasis (Acid homeostasis)
- Nephron is basic unit of kidney, 1-3 million of nephrons per kidney

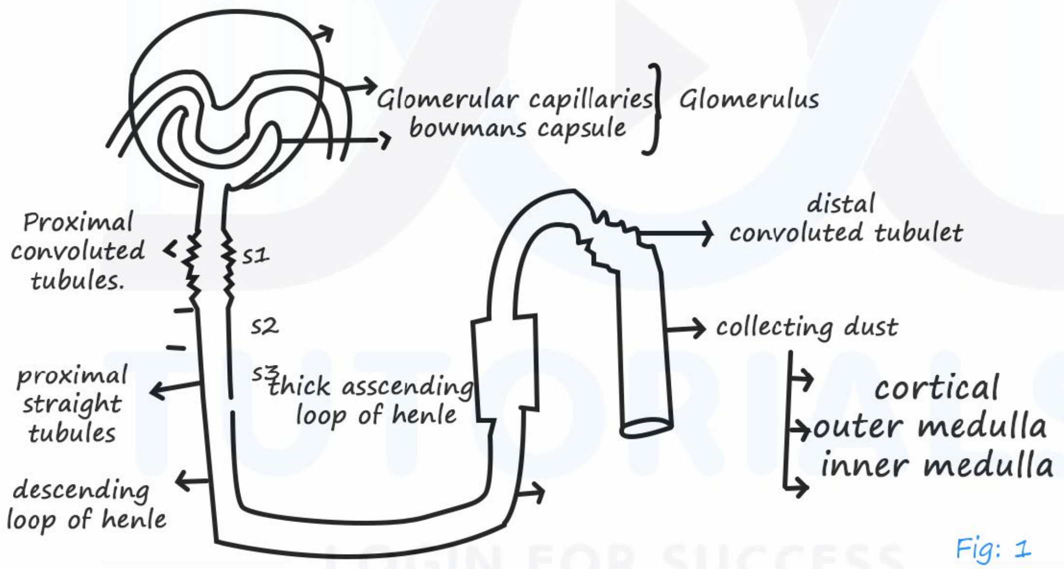

Glomerular capillaries
bowmans capsule
Glomerulus
Proximal convoluted tubules.
S1
S2
S3
proximal straight tubules
descending loop of henle
thick asscending loop of henle
distal convoluted tubulet
collecting dust
cortical
outer medulla
inner medulla

Fig: 1

- S3 located at corticomedullary junction therefore it is prone to ischemic injury

Proximal tubule	Distal tubule (i.e., DCT & CD)
Brush border (+) Therefore, maximal absorption	Absent
Carbonic anhydrase 284	Only carbonic anhydrase 2 is present, therefore acid in urine is not buffered
No acidification, therefore CA4 present	Acidification of urine occurs here
Leaky tight junctions Therefore, paracellular absorption occurs	Non leaky tight junction paracellular absorption does not occur

Nephron

Cortical | Juxta medullary

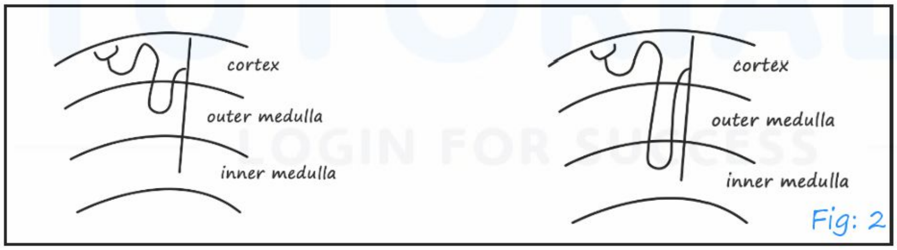


Fig: 2

Cortical	Juxta medullary
- 65% of total nephron	- 15% of total nephrons
- Short loop of Henle	- Long deep loop of henle
- More blood flows	- Less blood flows
- Main function excretion of waste products	- Main function concentration of urine

Glomerulus

Renal circulation 00:11:30

- 20% of Co goes to kidney i.e; 1250ml (Approx. 300g)
  - Cortex: 5ml/g/min
  - Outer medulla: 2.5 ml/g/min
  - Inner medulla: 0.6/g/min → low blood supply in medulla is important to maintain hyperosmolarity of medulla.
- A-V oxygen difference = 14ml/L of blood.
  - large O2 is needed by kidney for Na reabsorption

Glomerulus 00:15:00

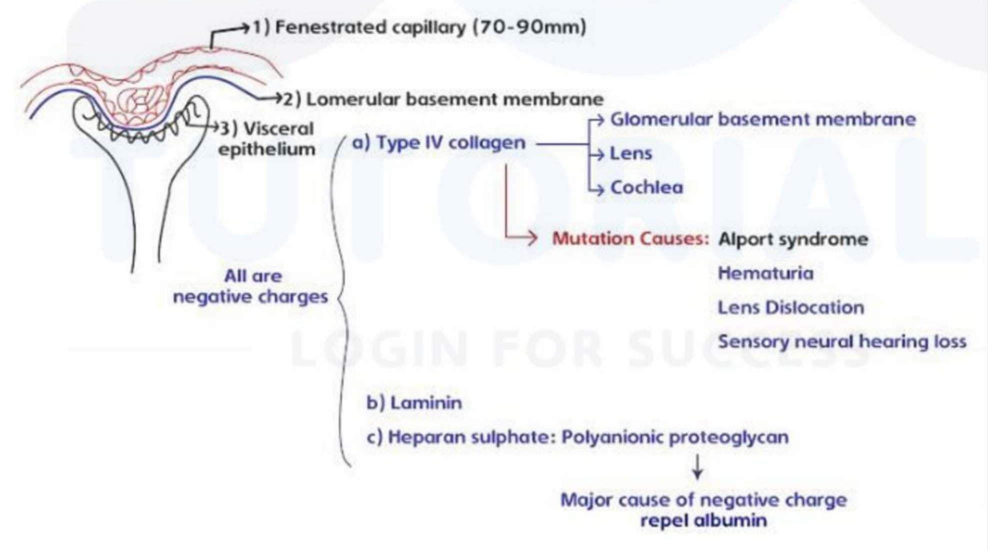

1) Fenestrated capillary (70-90mm)
2) Lomerular basement membrane
3) Visceral epithelium
All are negative charges
a) Type IV collagen
Glomerular basement membrane
Lens
Cochlea
Mutation Causes: Alport syndrome
Hematuria
Lens Dislocation
Sensory neural hearing loss
b) Laminin
c) Heparan sulphate: Polyanionic proteoglycan
Major cause of negative charge
repel albumin

Fig: 3

Visceral epithelium

- It is made of podocytes

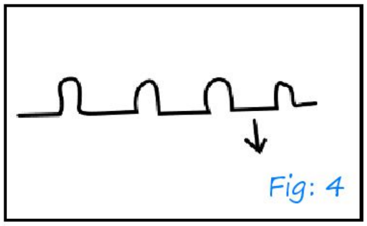


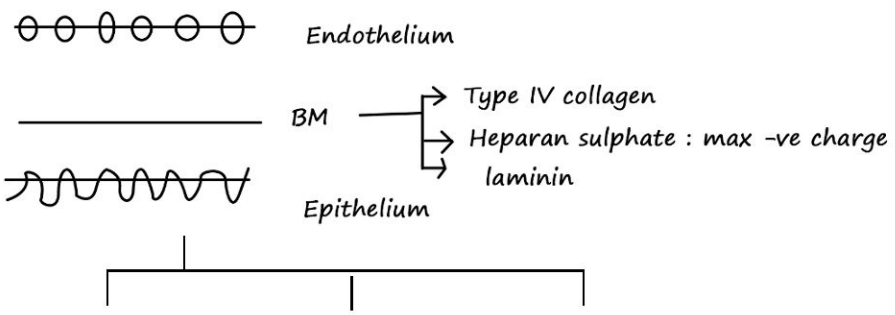
Fig: 4

- Filtration slit – (20-30nm)
  - For filtration of plasma
  - Synthesize glomerular basement membrane
- Loss of podocytes
  - FSGS (Focal segmental glomerulosclerosis)
  - Diabetic nephropathy

Proteins in slit diaphragm

- Nephrin/NPHS mutation → Congenital nephrotic syndrome of finish type
- Podocin/NPHS2 mutation → Steroid responsive nephrotic syndrome (Childhood type)
- Alpha actinin 4 mutation → Autosomal dominant FSGS

Summary


Endothelium
BM
Type IV collagen
Heparan sulphate : max -ve charge
laminin
Epithelium

Nephrin → NS

Podosin → SRNS

α Actinin 4 → AD-FSGS

GFR 00:26:00

- Kf x NFP

  Kf -Cannot be measured directly
- Kf – Filtration coefficient
- NFD – Net filtration pressure

$$Kf = \frac{GFR}{NFP} = \frac{125ml/min}{10mmHg}$$

$$= 12.5ml/min/mmHg$$

$$\text{Filtration fraction} = \frac{GFR}{\text{Renal plasma flow}} = 20\% = 0.2$$

Glomerular membrane permeability 00:28:10

- Size
  - Size <4nm freely filtered
  - 4-8nm – Filtration depends on charge

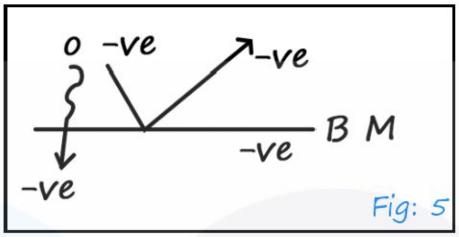


Fig: 5

  - >8nm not filtered at all
  - Album is first protein to get in urine in kidney disease
  - Effective molecular wt/size: 7nm
  - But not filtered due to negative charge
- GFR
  - GFR = Kf x NFP

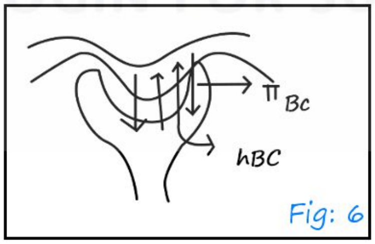


Fig: 6

- HGC: Hydrostatic pressure of glomerular capillaries
- πGC: Oncotic pressure of glomerular capillaries
- HBC: Hydrostatic pressure of bowman's capsule
- πBC: oncotic pressure in bowman's capsule

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NFP

- (hGC – hBC) + (πBC – πGC)
- (60-18) + (0-32)
- 42-32
- 10mmHg
- GFR = 12.5 x 10
- 125ml/min

Regulation of GFR 00:34:10

- Autoregulation
  - Myogenic
  - TGF – Tubulo glomerular feedback mechanism

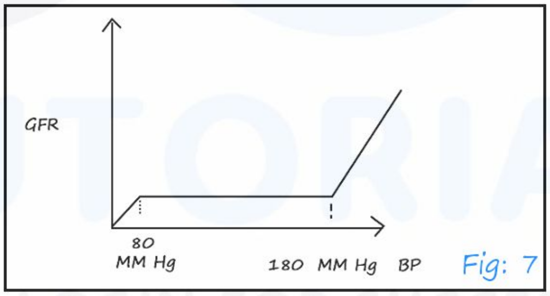

Fig: 7

- GFR remains constant between 80-180mmHg of MAP
- Because of autoregulation

Myogenic regulation

- Increases Blood flow
- Stretch at afferent arteriole (Sensor)

- Release of $Ca^{+}2$ from afferent arteriole
- Constriction of afferent arteriole
- Decreases Blood flow

TGF

- Sensor: Macula densa (Present in end of ascending loop of henle /Proximal DCT)
- Sense NaCl in thick ascending limb of LOH
- Adenosine is released
- Vasoconstriction of afferent arteriole
- ↓Blood flow
- Keep this as flow chart as written

Mesangial cell (intraglomerular) A/K/A stellate cell

Contraction	Relaxation
↓GFR	↑GFR
– Angiotension II	– Cyclic AMP
– Endothelin	– Nitric oxide
– Nor epinephrine	– ANP
– Adenosine	– Prostaglandins
– Thromboxane A2	– Dopamine
– ADH	

Change in resistance of afferent & Efferent arteriole

- Constriction of afferent arteriole – In shock due to norepinephrine both RPF & GFR ↓ mainly hypovolemic shock
- Dilatation of afferent arteriole – caused by prostaglandin, therefore ↑ NSAID ↓PG causing ischemic injury
  - PG increase blood flow in renal cortex & decrease in renal medulla
- Constriction of efferent arteriole – caused by angiotensin II

  EA >>> AA
  - Increased Hydrostatic pressure → GFR
  - Renal plasma flow ↓Due to sluggish blood flow → so GFR ↓
- Therefore, Initially GFR ↑ due to increase in hydrostatic pressure later GFR due to ↓ in RPF
  - Filtration fraction = $\frac{GFR}{RPF} = \frac{\uparrow\uparrow/\downarrow}{\downarrow\downarrow\downarrow}$

    FF always increases
  - Oncotic pressure increases due to accumulation of proteins in glomerular capillaries, due to ↑filtration fraction
  - Dilation of efferent arteriole – Angiotensin receptor blocker GFR↓ RPF ↑

- GFR↓: Work is decreasing
- RPF↑: ↑Nutrition
- They are nephroprotective
- Therefore, used in diabetic nephropathy

Note

- Increased Protein intake = ↑GFR

Therefore, Increased amino acid → More reabsorption of A.A/More reabsorption of Na^+ (in blood)

↓

Decreases Na in lumen

↓

Activation of RAAS → AT – II → Constriction of efferent arteriole

↓

↑GFR

- Increased Protein in blood = GFR decreases Due to increased oncotic pressure

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PCT

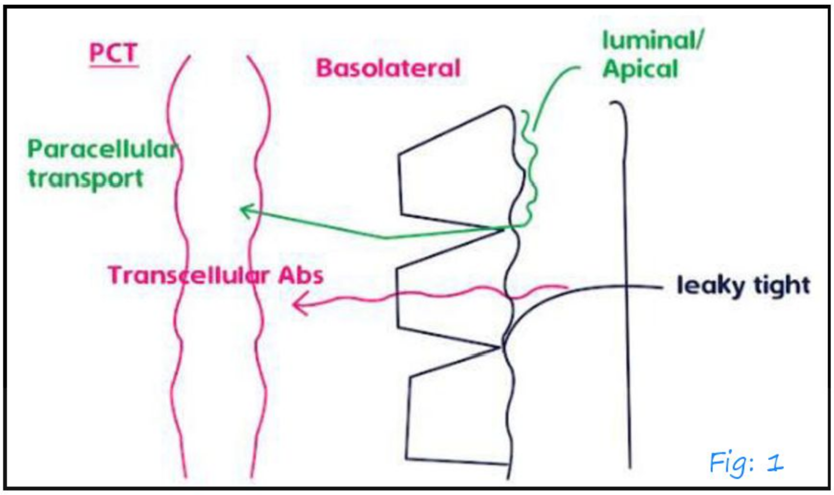
PCT
Basolateral
luminal/
Apical
Paracellular
transport
Transcellular Abs
leaky tight

Fig: 1

100% Reabsorption of glucose and amino acids

80% Reabsorption of Po_4 and HCO_3^-

70% Reabsorption of Ca^+

67% (2/3) Reabsorption of urea, Na, Cl^-, H_2O → via osmosis

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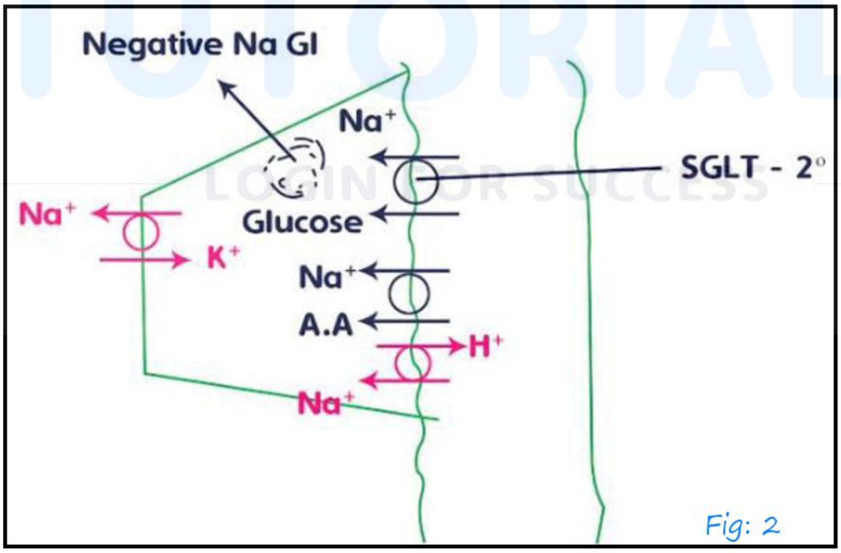
Negative Na Gl
Na⁺
SGLT - 2°
Na⁺
Glucose
K⁺
Na⁺
A.A
H⁺
Na⁺

Fig: 2

- Na^+ is absorbs via many transporters on apical membrane

  Example: Na Ammo Acid transporter

  Sodium Glucose transporter

- Maximum Na^+ absorption is via Na H antiporter
- H_2O – osmosis follows after Na^+ transport

  Therefore, in PCT urine is isosmotic due to osmotic drag occurring via aquaporin 1 (2/3 water absorption via this)

Fate of glucose in PCT 00:08:35

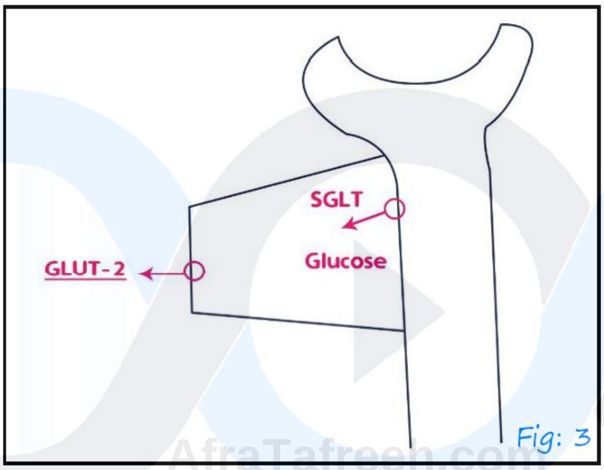

Fig: 3

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SGLT

- SGLT1
  ↓
  10% present in intestine
- SGLT2
  ↓
  90% glucose absorption absent in intestine

Therefore, SGLT2 blocker used to prevent glucose reabsorption

Example: Canagliflozin
Dapagliflozin
Empagliflozin

Side effects: UTI therefore taken with increase amount of water.

1.Filtered load of Glucose: GFR x plasma glucose concentration

= 125 ml/min x 80mg/dl

= 125 x 0.8 mg/ml

100 mg/min

2.T max (Transport Max): Maximum glucose absorption in kidney (PCT)

→ 375 mg/min

Therefore, normally no glucose passes beyond PCT.

Therefore 100% reabsorption.

3.Renal threshold of glucose: Minimum amount of glucose in blood, so that glucose can appear in urine

4. Real value: → 180-200 mg/dl

5. Calculated renal threshold of glucose $R_TGl = \frac{T\ max}{GFR} = 300$ mg/dl

Difference in actual renal threshold of glucose and calculated renal threshold of glucose is called splay

↓

Cause: Heterogenecity of nephron function

i.e. All nephrons have different reabsorption and filtration capacity

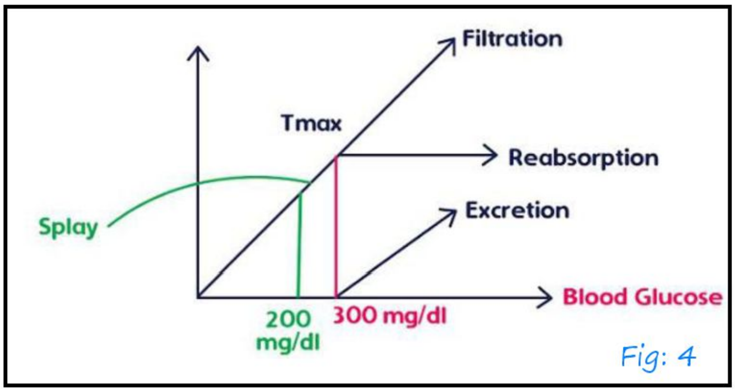

Fig: 4

Q: RBS – 230mg/dl

T max = 150 mg/min

GFR = 100 ml/min

How much glucose lost in urine?

Filtration fraction – GFR x Plasma conc

= 100ml/min x 230 mg/dl

= 230 mg/min

T max = 150 mg/min

Therefore, lost is 80 mg/min

Note:

$$\frac{\text{Tubular fluid concentration (TF)}}{\text{Plasma concentration (P)}} = 1 \text{ isotonic}$$

$\frac{TF}{P} < 1$ = Substance is reabsorbed more than H_2O

Example: Glucose Amino Acids

$\frac{TF}{P} > 1$ = Substance is absorbed < H_2O

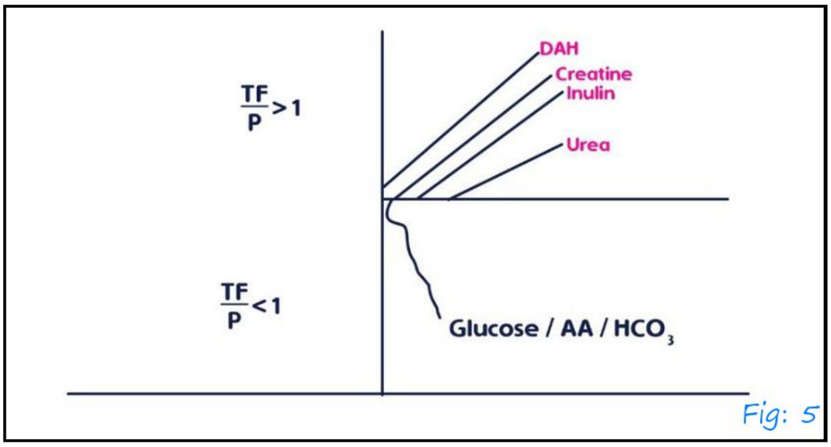

Fig: 5

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LOOP OF HENLE

Descending limb of Henle: 00:01:22

- Impermeable to solutes
- Permeable only to H_2O

↓

Reabsorbed

Aquaporin I

Transcellular reabsorption

@Concentrating segment of nephron

→ solution turns hypertonic

Thin ascending limb:

- Passive reabsorption of Na+ and cl

Thick ascending limb:

- Permeable to solutes
- Impermeable to H_2O (diluting segment of nephron

→ hypotonic)

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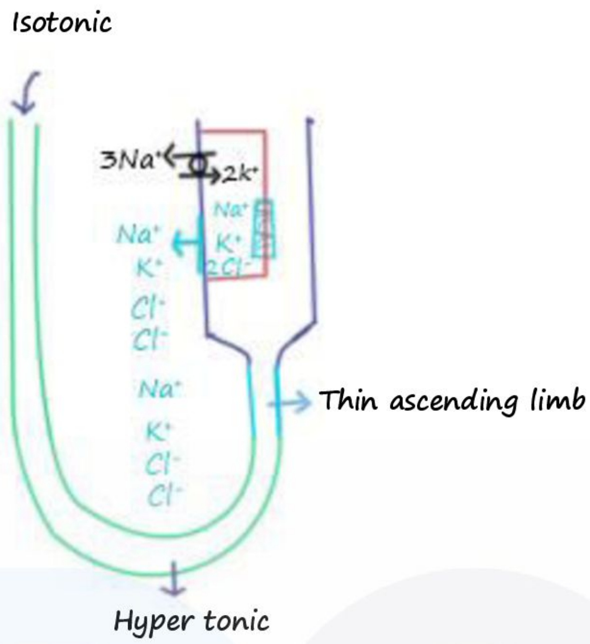
Isotonic
3Na⁺
2k⁺
Na⁺
K⁺
2Cl⁻
Na⁺
K⁺
Cl⁻
Cl⁻
Na⁺
K⁺
Cl⁻
Cl⁻
Thin ascending limb
Hyper tonic

Counter current mechanism 00:09:56

Ascending limb:

Fuses with neighboring

Vasa recta

↓

Venules

↓

Interlobular

↓

Arcuate vein

↓

Interlobar vein

↓

Renal vein which drains into IVC

- CCM starts only in juxta-medullary nephrons but not in cortical nephrons

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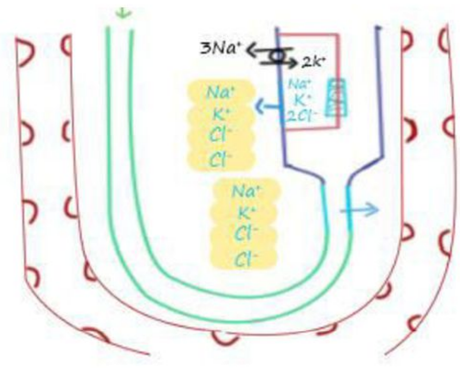


- Water exits from ascending limb and from descending limb of vasa recta
- The descending limb of vasa recta reabsorption solutes k^+, Na+, Cl) & loses water
- The fluid will be hypertonic / concentrated in the loop of vasa recta.
- When the fluid starts to move into the ascending limb of vasa recta, water from the interstitial enters ascending limb of vasa recta, due to high concentration, solutes start moving out.

Descending limb of vasa recta	**Ascending limb of vasa recta**
• Reabsorbs solutes • Looses H_2O	• Reabsorbs H_2O • Looses solutes

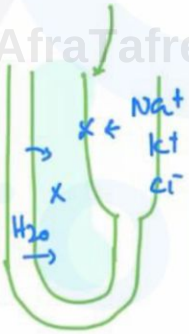
- Since thick ascending limb, Na+ - Kt -2 cl^- symporter are major initiators we call thick ascending limb as counter current multiplier.
- Vasa recta exchanges H20 from medullary interstitial → renal vein vasa is called as counter current exchange.

Clinical Correlation 00:26:40

Diuretic:

Furosemide:

- Blocks Na+ - K+ - 2cl symporter



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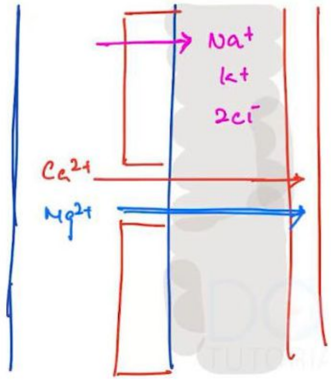
Reabsorption of calcium & magnesium in thick ascending limb:



- Na^+, cl^- K^2 – reabsorbed ~ 10-15 %
- Ca^{2+} → reabsorbed ~ 10 %]
  reabsorption is paracellular
- Mg^{2+} → ~ 60 -70 % in loop of Henle
- **Romk**- renal outer medullary potassium channels
- These channels again transport the reabsorbed potassium back to the lumen
- Ca^{2+} , Mg^{2+} → reabsorption occurs → by 2 forces
  - Concentration gradient
  - Electrical repulsion (K^+ ions in lumen)

Bartter's syndrome:

00:35:04

- Inactivating mutation of Na^+- k^+2cl^- – symporter makes defective reabsorption of Na^+, K^+ and Cl.

↓

Makes sodium and potassium to be lost in urine

Na^+ loss in urine
↓
H2O loss in urine
↓
Hypovolemia
↓
Reduced Systemic blood pressure
↓
Sensed by Granular cells (renal baroceptor)

k+ loss in urine
↓
hypokalemia

↓

Renin

↓

System blood (hyperhelium) angiotensin II

↓

Aldosterone → Na^+ reabsorption in collecting duct→

Increases systemic B. P

↓

Aldosterone

↓

Enhances H+ Secretion in collecting duct

↓

Alkalosis

- Barter's syndrome manifestation:
  - Hypovolemia
  - Hypokalemia
  - Alkalosis
- Differential diagnosis → Furosemide toxicity (overdose)

DISTAL CONVOLUTED TUBULE

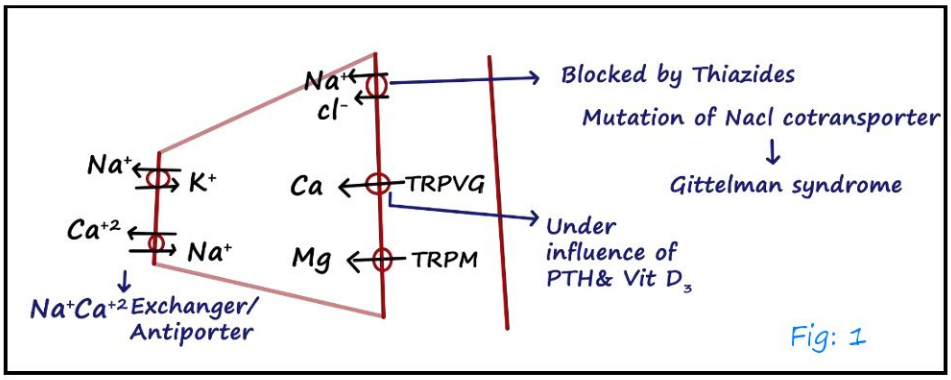

Na⁺
Cl⁻
Blocked by Thiazides
Mutation of Nacl cotransporter
↓
Gittelman syndrome
Na⁺
K⁺
Ca⁺²
Na⁺
↓
Na⁺Ca⁺² Exchanger/ Antiporter
Ca
TRPVG
Mg
TRPM
Under influence of PTH& Vit D₃

Fig: 1

Clinical features of Gittelman syndrome

1.Salt wasting + polyuria

2.Secondary hyper aldosteroneism

- Due to this normal blood pressure maintained

3.Due to increased aldosterone, hypokalemia occurs therefore K^+ is excreted in exchange of Na^+

4.Metabolic alkalosis (Therefore H^+ is lost in exchange of potassium)

5.This syndrome is associated with problem in Mg^{2+} transporter leading to hypomagnesemia

↓

In turn leading to decrease PTH release

↓

Hypocalcemia

↓

Tetany

6.There is gain in function of sodium calcium antiporter leading to increased absorption of Ca^{2+}. Therefore, No renal stones

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Bartter Syndrome	Gittelman Syndrome
Mutation of NKCC / ROMK) ClCkb / Barttin ↓ Mimic as loop diuretic	Mutation of Nacl symporter ↓ Mimic as thiazide diuretic
Polyuria, 2° hyper aldosteronism, hypokalemia, metabolic alkalosis	
-Renal stones, - Calcium clearance increases, Treatment: indomethacin	-Tetany → decrease Mg^{+2}, -Calcium absorption increases Treatment: $MgSo_4$ -better prognosis

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DOT TUTORIALS

Juxtaglomerular apparatus 00:11:20

↓ ↓

Near to glomerulus

Components

- JG cell: media of afferent arteriole
  Synthesize, store and released renin
  Since they have granules also known as granular cell
- They are baroreceptor hence sense renal hypotension (decrease BP) (or) renal hypoperfusion. (They have chemoreceptor function also)

- They have Beta 1 receptor and are stimulated by sympathetic system also.
- Macula densa:
  - Specialized epithelial cells in distal thick ascending limb of LOH / proximal DCT
  - They sense Nacl in thick ascending limb of LOH
  - They are chemoreceptor – regulate GFR by TGF mechanism (Tubulo-glomerulo feedback)
- Extraglomerular mesangial cells
  - Also known as lacis cells, goormaghtigh cell, polkissen cell
  - They are present between afferent arteriole and efferent arteriole.

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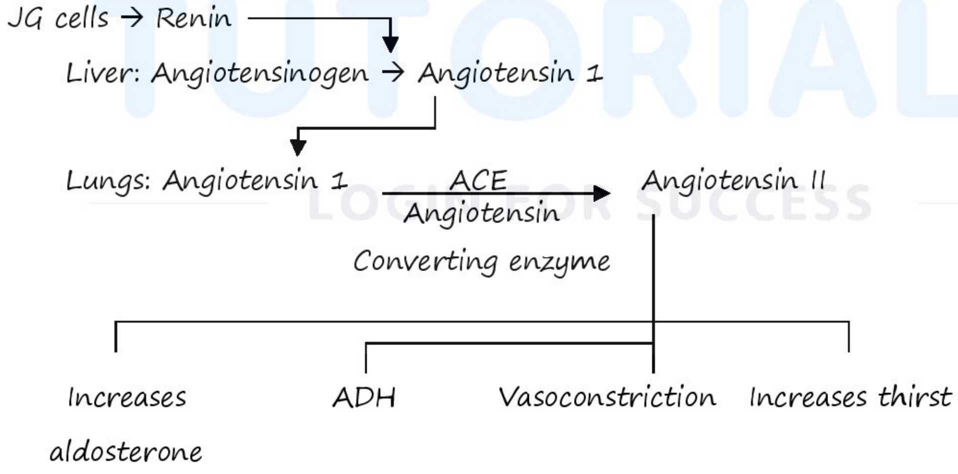
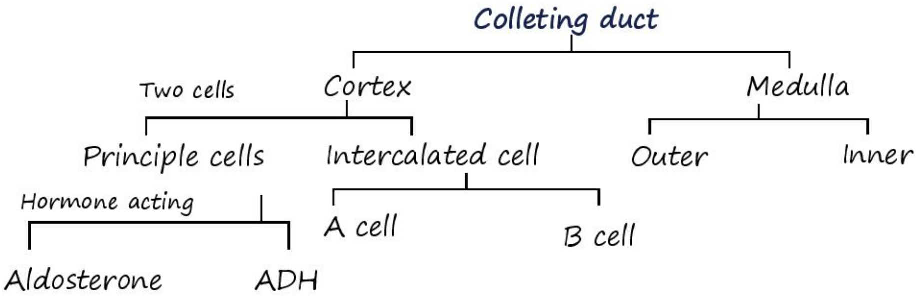
RAAS 00:18:55


JG cells → Renin
Liver: Angiotensinogen → Angiotensin 1
Lungs: Angiotensin 1
ACE
Angiotensin
Converting enzyme
Angiotensin II
Increases aldosterone
ADH
Vasoconstriction
Increases thirst

Overactive RAAS: Hypertension

Treatment: Direct renin blocker: Aliskiren.

COLLECTING DUCT


Colleting duct
Cortex
Medulla
Two cells
Principle cells
Intercalated cell
Outer
Inner
Hormone acting
A cell
B cell
Aldosterone
ADH

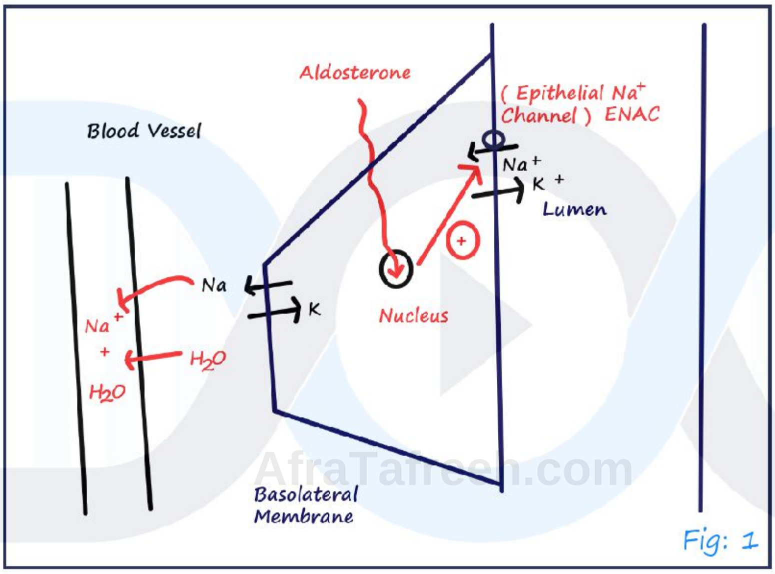

Aldosterone
(Epithelial Na^+ Channel) ENAC
Blood Vessel
Na^+
K^+
Lumen
+
Na
K
Na^+ + H_2O
H_2O
Nucleus
Basolateral Membrane

Fig: 1

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CONN syndrome

- Primary Hyperaldosteronism

↓

Increase Aldosterone

↓

Increase Na Reabsorption (But No edema)→ increase H2O

stimulate Right atrial receptors

HR increase
Decrease ADH
Increase ANP

] loss of water

it is called Aldosterone escape phenomenon

↓

Hypertension (Rennin suppressed)

- Rx: aldosterone antagonist E.g., spironolactone
  (K+ sparring diuretic)

DOC TUTORIALS LOOK FOR SUCCESS

Gain of mutation of ENAC

↓

CIDDLE Syndrome A/K/A pseudo Hyperaldosteronism

↓

Increases Na absorption

↓

- Hypertension
- Decreases renin
- Decreases aldosterone (In CONN Aldosterone K high)

- Treatmeent: ENAC blockers: Amiolardie
  Triamterne
  - Major stimulus for aldosterone release → hyperkalemia > H_2O depletion

ADH (Vasopressin)

↓

Synthesized by magnocellular neuron in

Supraoptic nucleus > paraventricular of hypothalamus

nucleus

- Stored & released from posterior pituitary

  "stored in form in herring bodies"

  ↓

  It has precurrosor of ADH called Neurophysim

Receptors (V)

i. V_{3A} = Vasoconstriction (Gq)

ii. V_{1B}/V_3 = A location: Anterior pituitary

↓

Release ACTH

iii. V_2 = location: principle cell of collecting duct

↓

Insertion of aquaporin II on apical/luminal side to increase water reabsorption

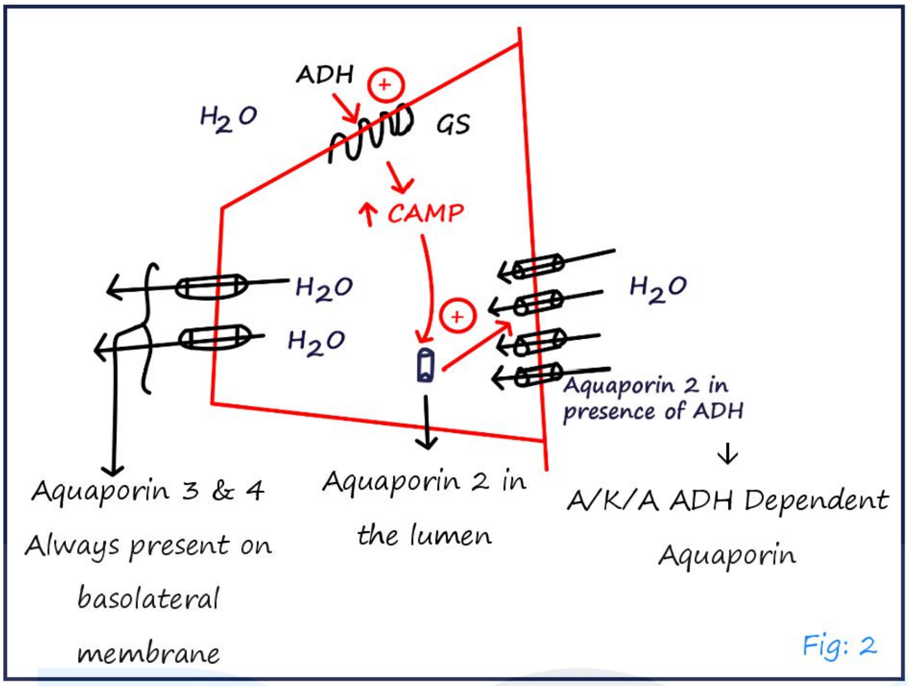
ADH
+
H_2O
GS
↑ CAMP
H_2O
H_2O
+
H_2O
Aquaporin 2 in presence of ADH
↓
A/K/A ADH Dependent Aquaporin
Aquaporin 3 & 4 Always present on basolateral membrane
Aquaporin 2 in the lumen

Fig: 2

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Factors

Increase ADH

- Decrease ECF volume
- Pain/emotions/stress
- Nausea /vomiting
- Angiotensin II

Decrease ADH

- Increase ECF volume
- Alcohol intoxication
- Note
  - ADH decrease: central Diabetes insipidus
  - ADH normal: mutation of V2/Aquaporin 2

    ↓

    Nephrogenic diabetes insipidus
  - Increase ADH: concentrated urine

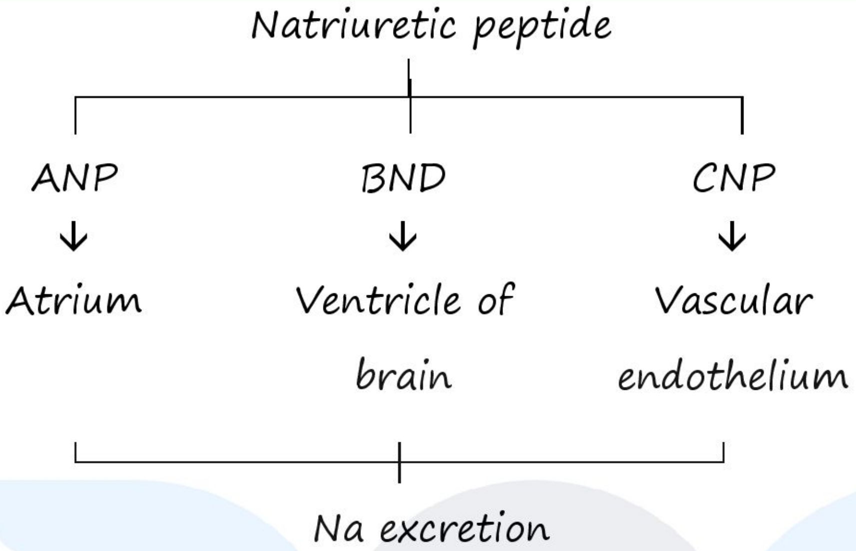
    ↓

    SIADH

    (Syndrome of inappropriate ADH secretion)

    Rx: V1, V2 antagonistic i.e vaptans canivaptan/Tolvaptan

Natriuretic Peptide 00:24:15


Natriuretic peptide
ANP
BND
CNP
Atrium
Ventricle of brain
Vascular endothelium
Na excretion

MICTURITION REFLEX, H_2O ABSORPTION CLEARANCE

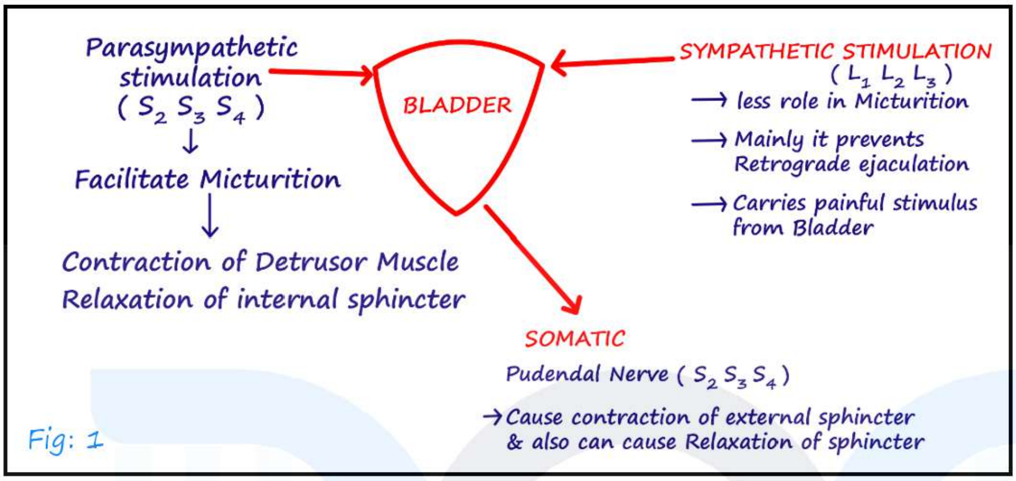

Parasympathetic stimulation
(S_2 S_3 S_4)
Facilitate Micturition
Contraction of Detrusor Muscle
Relaxation of internal sphincter
BLADDER
SYMPATHETIC STIMULATION
(L_1 L_2 L_3)
⟶ less role in Micturition
⟶ Mainly it prevents Retrograde ejaculation
⟶ Carries painful stimulus from Bladder
SOMATIC
Pudendal Nerve (S_2 S_3 S_4)
→ Cause contraction of external sphincter & also can cause Relaxation of sphincter

Fig: 1

Centres in Brain

00:03:50

- **PONS→** facilitate Micturition called Borrington's centre
- **Post hypothalamus:** Respond to clod
  - It increases frequency of urine
- **Inhibitory center** – Mid Brain
- **Cortex** – paracentral lobule

↓

Supplied by Anterior cerebral Artery

↓

Infraction leads to urinary Incontinence

(∴ voluntary control from cortex is lost)

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Cystometrogram 00:06:17

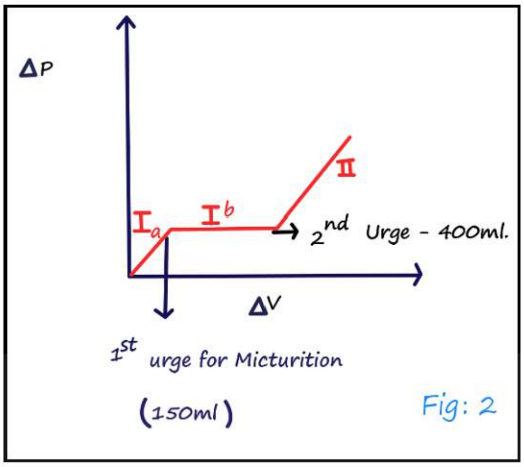


Fig: 2

Note:

Laplace law $p = \frac{2T}{R}$

With equal increase in Tension & radius, pressure remains constant

Ia: filling of Bladder → increase in pressure

Ib: Bladder is filling → pressure is constant ∴ volume is also increasing i.e., radius is increase

II: sharp rise in pressure – urge to micturate

- Ureteric peristalsis is due to pace maker Activity of smooth Muscles of Renal pelvis
- Relaxation of perineal Muscle for Bladder filling

↓

Bladder full

↓ contraction of Detrusor Muscle

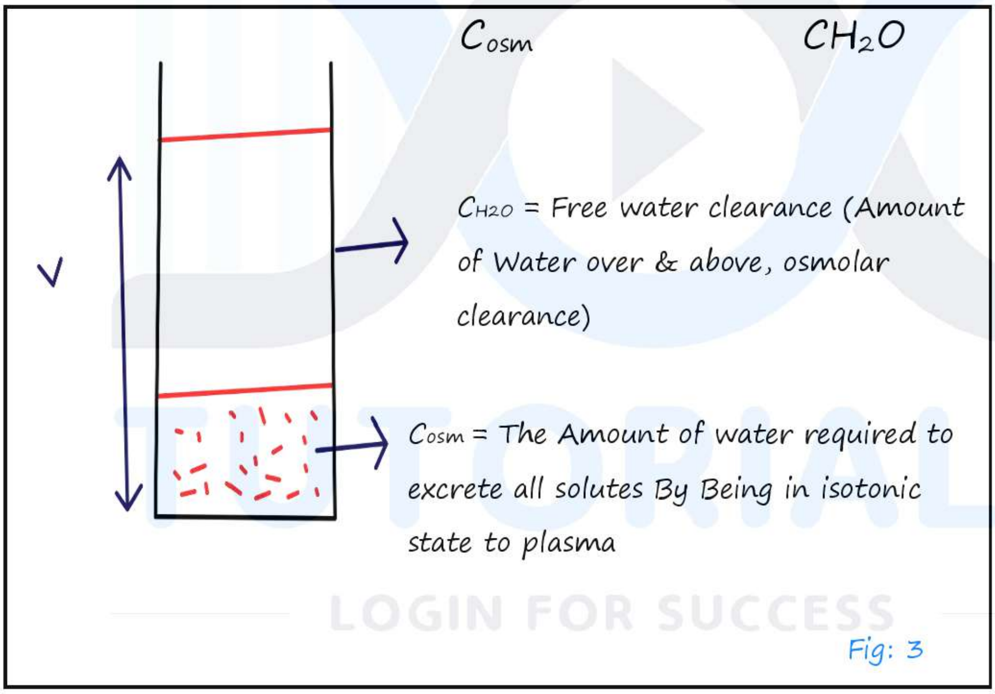
Micturition Reflex

Micturition Reflex

Water Reabsorption 00:10:55

Obligatory	Facultative
2/3 (or) 67% Water absorption ↓ Occur at PCT	1/3 (or) 33% water Absorption at DCT +CD

- Total amount of urine V= Osmolar clearance + Free water



C_{H_2O} = Free water clearance (Amount of Water over & above, osmolar clearance)

C_{osm} = The Amount of water required to excrete all solutes By Being in isotonic state to plasma

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Fig: 3

- Urinary osmolarity (Uosm) = plasma osmolarity (Posm)

  Then CH_2O (free water clearance)= 0
- Uosm > Posm then CH_2O= -ve (i.e., urine is more concentrated seen in SIADH
- Uosm < Posm than CH_2O = +ve (excess water in urine) e.g.: - Diabetes insipidus

Clearance 00:16:15

- Volume of plasma from which a substance is cleared in a given time is called clearance

$$\boxed{\text{Clearance} = \frac{U_s \times V}{P_s}}$$

Us - substance concertation in urine
V - Urine flow rate
Ps - substance concentration in plasma

- Filtration fraction (FF)= $\frac{\text{GFR (Glomerular Filtration rate)}}{\text{RPF}}$ = 20%

- $\frac{\text{? clearance}}{\text{RPF}} = \frac{\text{GFR + secretion – Reabsorption}}{\text{RPF}}$

Clinical conditions

- If a substance is fully filtered, neither reabsorbed nor secreted

$$\boxed{\text{Clearance} = \text{GFR}}$$

e.g.: - i. inulin ∴ Best to measure GFR
ii. creatinine clearance is used as surrogate Marker to measure GFR

it is not absolute marker because, it is slightly secreted

i.e., creatinine clearance > GFR

∴ 2nd Best Marker

- If a substance is fully filtered, fully secreted, not reabsorbed

Clearance= renal plasma flow (RPF)

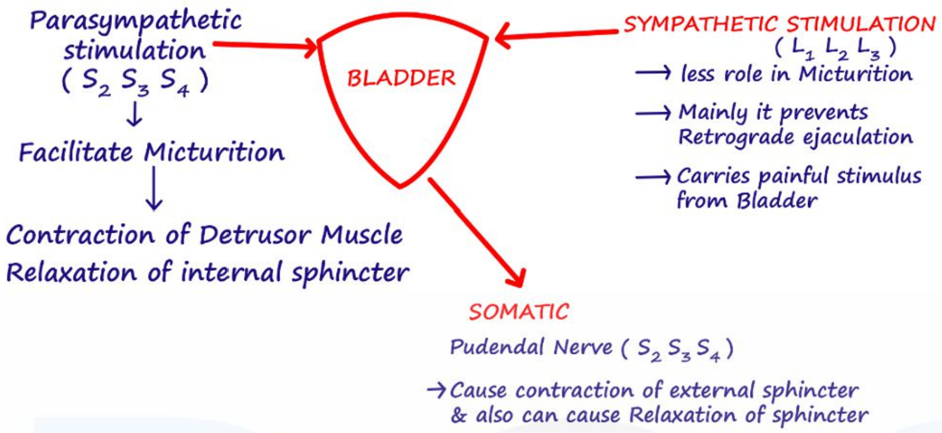
E.g., PAHA (para ammino Hippuric Acid)

↓

used to measure RPF within limited concentration

$$RPF = \frac{\text{Effective RPF}}{\text{Extraction ratio}}$$

MICTURITION REFLEX


Parasympathetic stimulation
(S_2 S_3 S_4)
Facilitate Micturition
Contraction of Detrusor Muscle
Relaxation of internal sphincter
BLADDER
SYMPATHETIC STIMULATION
(L_1 L_2 L_3)
⟶ less role in Micturition
⟶ Mainly it prevents Retrograde ejaculation
⟶ Carries painful stimulus from Bladder
SOMATIC
Pudendal Nerve (S_2 S_3 S_4)
→ Cause contraction of external sphincter & also can cause Relaxation of sphincter

---

Centres in Brain 00:03:50

- PNS→ facilitate Micturition called Barrington's centre
- Post hypothalamus: Respond to clod
  - It increases frequency of urine
- Inhibitory center – Mid Brain
- Cortex- paracentral labule

↓

Supplied by Anterior cerebral Artery

↓

Infraction leads to urinary

Incontinence (∴ voluntary control from cortex is lost)

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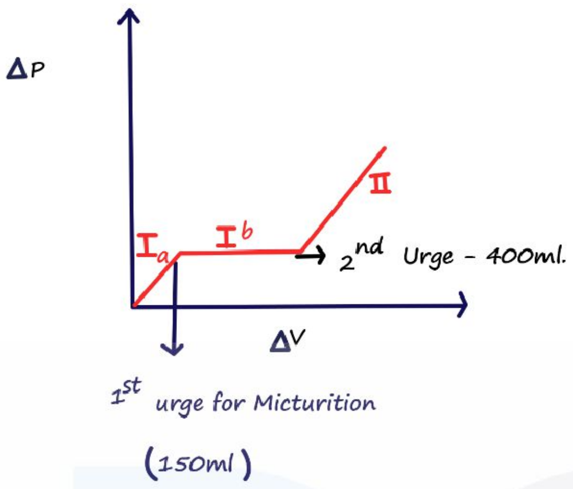
Cystometrogram 00:06:17



Note:

Caplace law $p = \frac{2T}{R}$

With equal increase in Tension & radius pressure remains constant

Ia: filling of Bladder → increase in pressure

Ib: Bladder is filling → pressure is constant ∴ volume is also increase in i.e., radius is increase

II: sharp rise in pressure – urge to micturate

- Ureteric peristalsis is due to pace maker Activity of smooth Muscle of Renal pelvis
- Relaxation of perineal Muscle for

Bladder full
↓
Bladder full
↓ contraction of Detrusor Muscle
Micturition Reflex

Micturition Reflex

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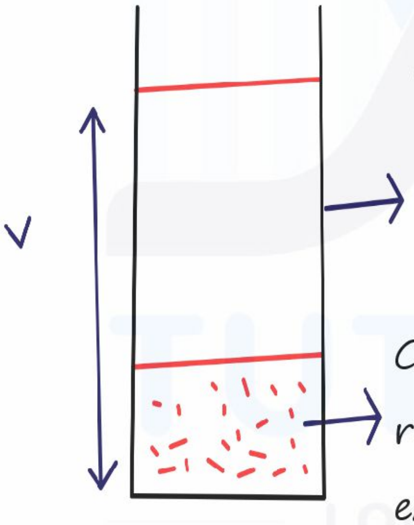
Water Reabsorption 00:10:55

Obligatory	Facultative
2/3 (or) 67% Water absorption ↓ Occur at PCT	1/3 (or) 33% water Absorption at DCT +CD

- Total amount of urine V= Osmolar clearance + Free water



CH_2O CoSm

CH2O = Free water (Amount ARY Water over

CoSM= The Amount of water required to excrete all solutes By Being in

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- Urinary osmolarity (UoSM) = plasma osmolarity (PoSM)

  Then CH_2O 9fre water clearence0= 0
- UoSM > PoSM than CH_2O= -v (i.e., urine is mor concentrated seen in SIADH
- UoSM < PoSM than CH_2O = +ve (excess water in urine) e.g.: - Diabetes insipidus

Clearance 00:16:15

- Volume of plasma from which a substance is cleared in a given time is called clearance

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i.e., creatinine clearance > GFR

∴ 2^{nd} Best Marker

- If a substance is fully filtered, fully recreated, not reabsorbed

Clearance= renal plasma flow

E.g., PAHA (para ammino Hippuric ACID)

↓

used to measure RPF with in limited concentration

$$RPF = \frac{\text{effective RPF}}{\text{Extraction ratio}}$$

ACID BASE BALANCE

- $H^+ \sim 0.00004$ meq/L

  $\sim 0.0000000\ 4$eq/L

- Log $H^+ = -7.4$

  $-(\text{Log } H^+) = 7.4$

  ↓

  $P^H = 7.4$ → negative log value of H^+

  (7.35 – 7.45)

  Slightly alkaline

- If $H^+ = 1/10 = p^H = -\log 1/10 = +1$

  $= 1/100\ p^H = -\log 1/100 = +2$

  $1/1000\ p^H = -\log 1/1000 = +3$

  $10-9 \qquad p^H=9$

- If $p^H > 7.8$ and < 6.9 → dangerous → not compatible with life

  ↓

  - Enzymatic activity and structure of proteins
  - Change in p^H → degenerative changes

- If p^H is low – acidity → excitability decrease
- p^H in high – alkalosis → excitability increase
- Most abundant p^H in body – protein, it can attach to H^+ and ca

Fig: 1

- If there is metabolic alkalosis

1.

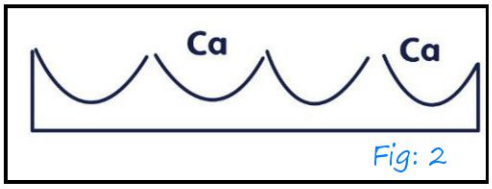

Fig: 2

↓↓

Proton decrease

↓↓

Protein will have free space

↓↓

More calcium is in bounded form

Free calcium is less → Hypocalcemia

↓↓

Voltage gated sodium channels are surrounded by calcium

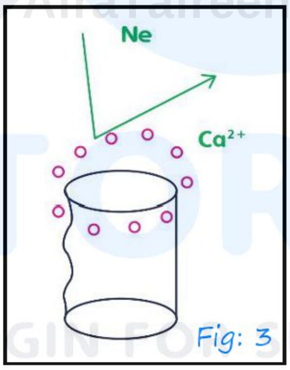

Fig: 3

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Free calcium decreases → stability decrease (excitability increase)

2.If there is metabolic acidosis → increase proton

↓

Increase free ca^{+}

If voltage gated Na channel surrounded by lot of calcium → entry of sodium less

↓↓

Stability increase (excitability decrease)

Henderson hasselbach equation

- $P^H = pka + \log \frac{Hco}{Co_2} \left(\frac{Base}{Acid}\right)\left(\frac{A^-}{HA^-}\right)$

  $Pka = 6.1$

- Buffering system works best when Pka of p^H

  Hco_3 → maintained by

  - Kidney → H_2o

  - Lung → Co_2

Regulation of H^+ 00:14:21

---

1. 1st line defence → chemical → buffer (within seconds)
2. 2nd line defence – respiratory → within mins
3. 3rd line defence – kidney → acts very slow

$$\downarrow\downarrow$$

$$Gain = \frac{correction}{Error} = \quad = \frac{00}{0}$$

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Buffer

- Weak acid with conjugate base

  (or)

- Weak base with conjugate acid
- Buffer can release H^+ or bind H^+ reversibly, so that free ion can be minimized
- Act by converting strong acid → weak acid
- Buffer + strong base – weak base

1. Hco_3 → present in ECF / plasma

- Weak acid → H_2co_3
- Base → Hco_3^- ($NaHco_3^-$)

A. $HCL + NaHco_3 \rightarrow H_2co_3 + Nacl$

↓ ↓

Strong acid weak acid

H_2O Co_2

↓ ↓

released from kidney released form lungs

B. $NaOH + H_2co_3 \rightarrow NaHco_3 + H_2O$

↓ ↓ ↓

Strong base used up weak base

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- Hco_3^- is most powerful buffer (pka =6.1 pH – 7.4)

↓

- H_2O → Kidney
- CO_2 → Lugs

2.Phosphate

WA WB

↓ ↓

$Na\ H_2\ po_4$ HPO4 (Na_2 $H+Po_4$)

↓

$Hcl + Na_2$ HPo_4 =

↓

strong acid

NaH_2PO4 + Nacl

↓

NaOH + weak acid

Na_2PO_4 → $Na_2 HPO_4$ + H_2

↓ ↓

SB WB

pH = 7.4

pka – 6.8 → phosphate

good buffer

- Most important buffer of ICF / tubular of fluid in kidney

3.Protein buffer

- Due to high concentration – most important intracellular buffer
- Imidazole group and α AA → pka within range of pH
- In RBC ~ Hb → major buffer due to → 38 histidine residues
- Deoxy Hb → better buffer

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Respiratory regulation of acid base 00:28:00

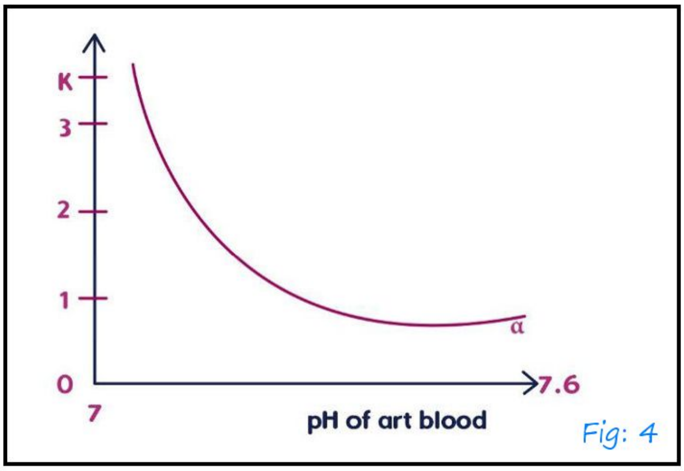

Fig: 4

- If there is respiratory acidosis, there is compensatory respiratory alkalosis
- If there is metabolic alkalosis, there is compensatory respiratory acidosis by causing Co_2 retention
- If pH decreases 7.4 to 7

  Acidosis → RR increase 4-5 times for compensation

  Gain = 75% ~ 3
- Of 7.4

  ↓ → RR decrease, Co_2 retained

  7.6

Renal regulation 00:31:24

- Only route which can excrete 80 meq of acid
- Approximately, we have 4400 meq of acid

  ↓

  4320 is buffered by bicarbonate in kidney

  Remaining 80 is excreted

  Excrete acidic urine | Excrete basic urine

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Excrete acidic urine

1.Reabsorption of filtered HCo_3^-

- Happens in PCT → not in collecting in CD

  ↓

  No CA IV

  Has only CA II

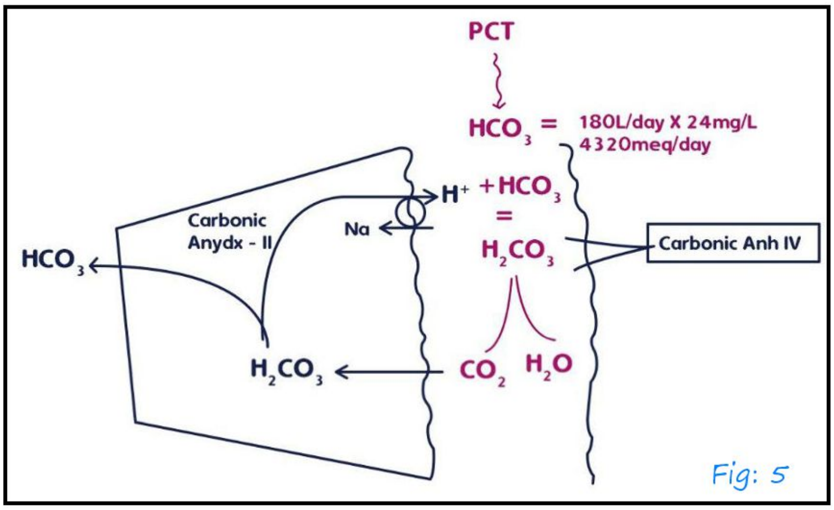
PCT
HCO_3 = 180L/day X 24mg/L
4320meq/day
H^+ + HCO_3
=
H_2CO_3
Carbonic Anh IV
CO_2
H_2O
Na
Carbonic Anydx - II
HCO_3
H_2CO_3

Fig: 5

- In PCT, No acidification of urine happen
- (DCT → absence of CA – IV → acidification of urine happens → CD

  CD
  ↓
  Intercalated cells
- Limiting pH → H^+ secreted in urine → limit pH = 4.5

1	2
Reabsorption of HCO_3 from PCT	Acidification of urine in CD
Defective ↓	
Type II renal tubular acidosis → metabolic acidosis due to	Defective acid of urine
defective Hco_3 absorption	Renal tubular acidosis type I

RTA – Type IV

- Due to decrease aldosterone (Aldosterone causes Na-water absorption and potassium secretion)
  Increase hyperkalemia
  ↓
  Metabolic acidosis

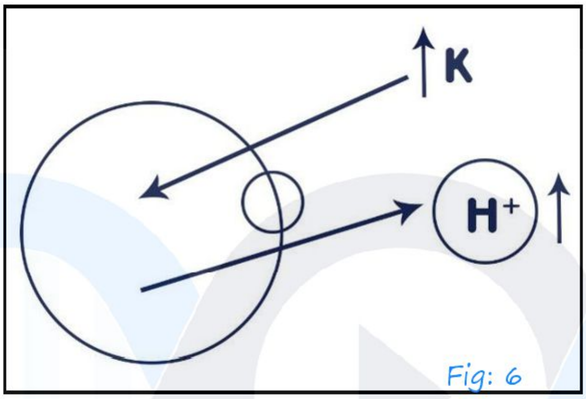

Fig: 6

Hyperkalemia – Tall tented T waves

2.H^+ excretion → titrable - Po_4 and NH_3

$H^+ + HPO_4 = H_2PO_4$

$+ NH_3 – NH_4 cl.$

3.Generation of new HCo_3^-

- $Po_4 \rightarrow H_2 Po4$
- $NH_3 \rightarrow NH_4cl$

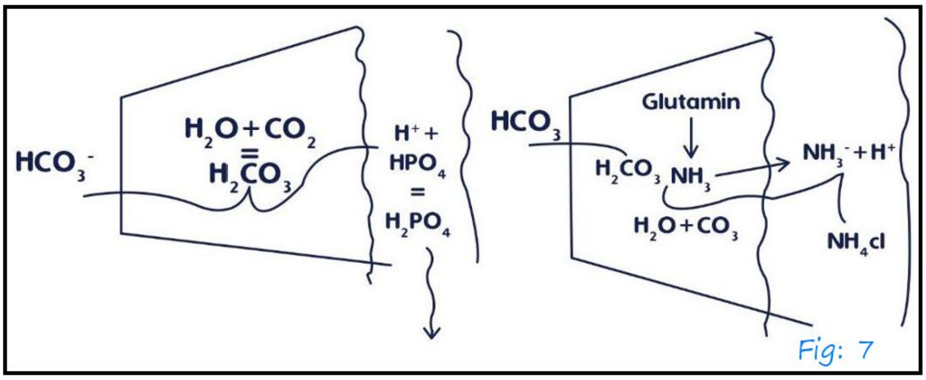
HCO_3^-
H_2O+CO_2
H_2CO_3
$H^+ +$
HPO_4
=
H_2PO_4
HCO_3
Glutamin
H_2CO_3 NH_3
$NH_3^- + H^+$
H_2O+CO_3
NH_4cl

Fig: 7

Anion gap 00:48:42

- Number of anions = number of cations
- Cations can be measured completely
- In anion phase, either bicarbonate or chloride in measured → measured anion

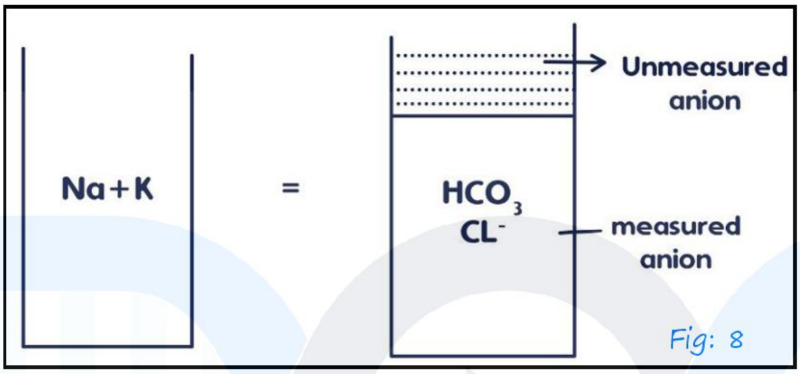
Na+K
=
HCO_3
CL^-
Unmeasured anion
measured anion

Fig: 8

$AG = Na + K - (Hco_3 + cl^-) \rightarrow 10\text{–}20\ meq/L$

$Na + (Hco_3 + K) - (8\text{–}16\ meq/L$

- If there is metabolic acidosis

Failure to excrete
↓
CRF

Loss of Hco_3
↓
- Diarrhea
- vomiting of intestinal content RTA (2)

Addition of acid
↓
lactic acidosis

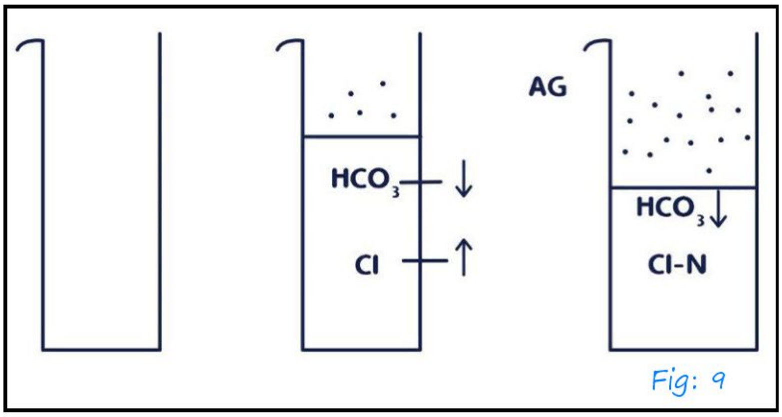
AG
HCO_3 ↓
Cl ↑
HCO_3 ↓
Cl-N

Fig: 9

- Metabolic acidosis – 2 types

hyperchloremic metabolic acidosis → NAGMA

- Diarrhea
- RTA
  - –I → Defective reacidification of urine
  - –II → defective Hco_3 reabsorption
  - – IV → increase K

Normochloremic metabolic acidosis → HAGMA

NAGMA

- H – Hyperalimentation
- A – Acetazolamide
- A – Amphotericin B
- R – RTA
- D – Diarrhea
- U – ureteral diversion
- P – pancreatic fistula
- S –spironolactone / saline

HAGMA

- M – methanol poisoning

- U – uremia
- D – DKA
- P – Paraldehyde / Propofol
- I – Ischemia – Iron / IN / IE of metabolism
- L – Lactic acidosis
- E – ethylene glycol
- S – Salicylates / starvation
- C – CO | CN |CHF
- A – Aminoglycoside
- T – Theophylline and Toluene

- If there is metabolic acidosis, there will be compensation by

  respiratory alkalosis

  ↓↓

  By increase RR, Co_2 wash out

- In DKA, increase RR → kussmaul breathing
- Expected $Paco_2$ – $(1.5 \times HCo_3 + 8) \pm 2$

  Normal $HCO_3 = 24\ (15 + 8) \pm 2$

  $MA = 10\ 23 \pm 2$

Respiratory acidosis

- When $Paco_2 > 42$ mmHg

  1°   2°

  - Respiratory depression like opioids and trauma
  - Respiratory muscle- polio and GBS

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- CO_2 retention → compensated by metabolic alkalosis HCO_3 increase

Metabolic alkalosis

- $HCO_3 > 26$ mm/L
- Compensated by respiratory acidosis

$$\begin{aligned} PaCO_2 &= ((0.7 \times HCO_3)-24) + 40 \\ &= ((0.7 \times 40) - 24) + 40 \\ &= (28-24) + 40 \\ &= 44 \end{aligned}$$

RECEPTOR PHYSIOLOGY

- Paracrine – one cell stimulating other cell
- Autocrine – one cell stimulates its own self
- Endocrine- cell going to blood circulation and stimulating distant organ or cell or tissue
- Term endocrine given by Starling
- 1st hormone to be discovered was secretin by Bayliss and starling

5 Types of Hormones 00:02:33

- Amino Acid derivatives
- Small neuropeptide
- Large neuropeptide/pH
- Steroid
- Vitamin A.D

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Amino Acid derivatives

- Tyrosine - Thyroid
  - Epinephrine
  - Norepinephrine
  - Dopamine
- Tryptophan – serotonin
  - Melatonin
- Histidine – Histamine

Small Neuropeptide

- TRH- Glutamate + Histidine + proline
- GnRH- 10 AA
- Vasopressin Oxytocin – 9AA

Large neuropeptides /protein homes (> 50AA)

- Pituitary gland
- Pancreases + Erythropoietin
- Parathyroid

→ Synthesized in RER and modified in Golgi apparatus

  - No of A in insulin – 2
  - No of AA in PTH – 84

Steroid Hormone

- Basically cholesterol
- Synthesized in – adrenal cortex
  - Ovary
  - Testis
  - Placenta
  - Smooth ER
- C21 → progestins /corticoids
- C19 → testosterone
- C18 →
- All hormones have entered the nucleus either directly or through cell messenger DNA converted to RNA, RNA converted to protein
- If they are protein and cannot get in to cell membrane, their receptor will be in the cell

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membrane, and called as cell membrane receptors

like – AA ligand
- Protein ligand

- If they can enter inside, they have receptor in cytoplasm/nucleus
  ↓ Cytoplasmic
  ↓ Nuclear

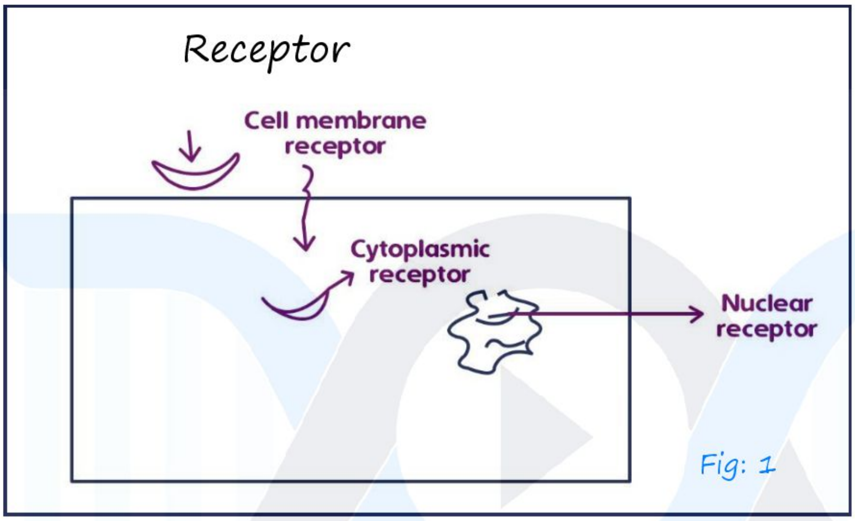
Receptor
Cell membrane receptor
Cytoplasmic receptor
Nuclear receptor

Fig: 1

Cell membrane receptor

- GPCR
- Receptor tyrosine kinase
- TAKE or JAK SATA or Cytokines
- R serine/threonine kinase

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- GPCR → G protein coupled receptors
  → largest family of receptors
  → Also called serpentine receptor or seven pars' receptors
  ↓

Nobel prize was given of this discovery in 1994 to Alfred Gillman

- Broadly divided → G stimulatory (GS)
  → G inhibitory (Gi)
  → Gq

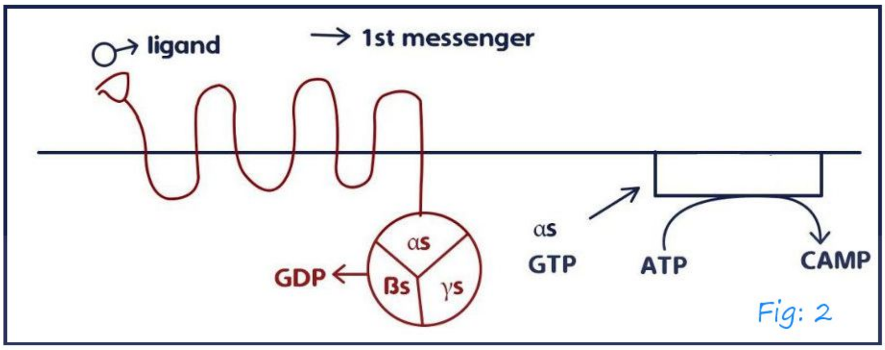

Fig: 2

- Ligands are any chemical which attach to the receptor to do some biological action
- When ligand attaches

  ↓

  GDP converted to GTP

  ↓

  α s takes up GTP and reaches Adenyl cyclase

  ↓

  Adenyl cyclase with help of α s GTP coverts ATP → CAMP (2nd messenger)

  ↓

  Cause phosphating of protein → does multiple physiological action depending on ligand 2 location n

  ↓

  Kinase A

  ↓

  Tertiary messenger

- CAMP → AMP

  ↓

  Phosphodiesterase

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- α s has intrinsic GTPase activity → converts all GTP → GDP

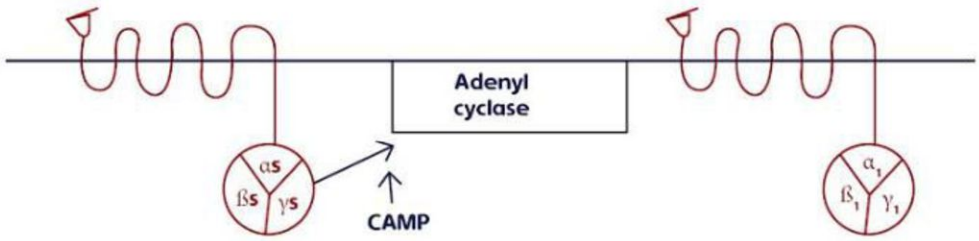
Adenyl cyclase
αs
βs
γs
CAMP
α_1
β_1
γ_1

Fig: 3

- Adenyl cyclase in sandwiched between GS and H
- α → Adenyl cyclase

  ↓

  Increase CAMP

  ↓

  phosphating of protein kinase A
- α i → Adenyl cyclase

  ↓

  Decrease CMP

  ↓

  Dephosphorylation of protein kinase A

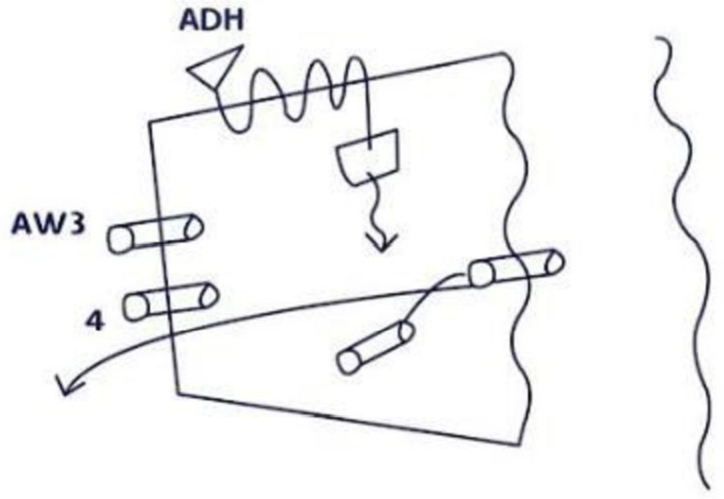

Fig: 5

- e.g.: when ADH combines with GS → enter then cell

↓

Implants aquaporins on sides of Lumen

↓

Water is absorbed

- In heart, B1-GS → increase CAMP → increase HR

M2 - G1 → decrease CMAP → decrease HR

Cholera toxin → 2 units

A

Monomeric enzymatic moiety → Active

↓

ADP Ribosylation of GSα

↓

Continuous activation of adenyl cyclase

↓

Increase CAMP

↓

Phosphorylation of protein (FTR gene) → cystic fibrosis transmembrane receptor

↓

Chloride channel

↓

Increase choired secretion in human of intestine

↓

Na/H2O → diarrhea

B

Binding unit → pentameric

↓

Binds with Gm, ganglioside in intestinal epithelia cell

↓

- ONN → permanently ONN
- Pertusis toxin → inhibit Gα 1→ increase CAMP

↓

Increase secretion

↓

Whopping cough

- ON switch parament ON – cholera toxins
- Off switch OFF means – peritries

Increase adenyl cyclase

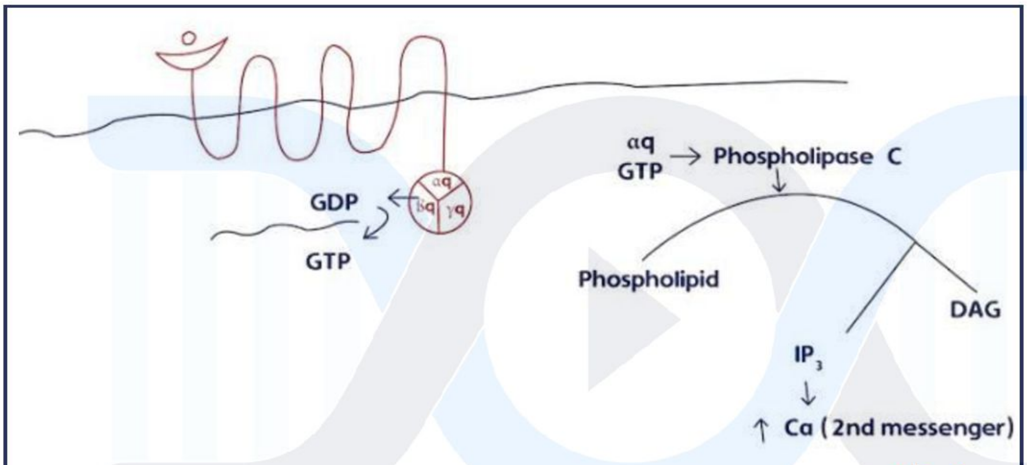
αq
GTP
→ Phospholipase C
GDP
GTP
αq
βq
γq
Phospholipid
DAG
IP$_3$
↑ Ca (2nd messenger)

Fig: 6

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Example

- Gs → – ADH (V2 –CD)
  - Epinephrine /(P1)
  - Norepinephrine
  - Glucagon
  - TSH/FSH/ACTH/PTH/MSAH/corticotropic releasing hormone /secretin/calcitonin
  - β1/β2/β3→ Adrenergic

- Gi → – somatostatin
  - Angiotensin II

  - α 2
  - Muscarine (M2, M4)
- Gq→ - All releasing hormone except GRH
  - TRH/GnRH/oxytocin/CCK
  - M1, M2, M5

Diseases due to mutation in GPCR

Mc cure Albright syndrome

- Gain of mutation of GS α
- 3P's – precocious puberty (due to gonadotrophins)
  - Polyostotic fibrous dysplasia (PTH)
  - Pigmentation (MSH)
  - Pseudohypoparathyroid

PITUITARY GLAND

Pituitary gland
↓
Pituitary → Master gland

Releasing hormones

These are secreted by hypothalamus

1.TRH
  - TSH
  - Prolactin

2.CRH → POMC
  - ACTH
  - β lipotrophin

3.GNRH
  - FSH
  - LH

4.GHSH
  - Increases GF

Inhibitory hormones

1.Prolactin inhibitory hormone / Dopamine = decrease prolactin

2.GHIH = decrease growth hormone

Pituitary necrosis → increase prolactin is seen.

Anterior pituitary 00:04:35

Acidophilic	Basophilic
• Lactotrophs → prolactin	• Gonadotrophs (20%) → FSH and LH
• Somatotrophs → GH (50%) (maximum)	• Corticotrophs (10%)
	• Thyrotrophs (5%)→ TSH

Growth hormone 00:07:10

- Most abundant hormone of anterior pituitary gland
- GH release is pulsatile
- T1/2 – 6-20 min

Increased growth hormone	Decreased growth hormone
• Stress	• Cortisol
• Hypoglycemia	• Hyperglycemia
• Fasting / exercise	
• NREM sloop	• REM
• Protein meal	• IGF
• Glucagon and ghrelin	

Pituitary → Growth Hormone → Indirect effect in liver

↓ ↓

Direct effect
↓
JAK – STAT Receptor
- Lipolytic

somatomedins (Insulin like growth factors)
↓
receptor tyrosin kinase
antilipolytic

In bone cause differentiation and proliferation of cartilage cell. In epiphysis (end plate of long bones – similar action)

- Increase size of viscera
- Increase insulin resistance

GH: – supplementation causes lipolysis and protein anabolism

- Hyperglycemic hormone →
  - Increase reactions which increase glucose
  - inhibit reaction which decrease glucose
- Glycogenesis decrease (Glucose to glycogen)
- Glycogenolysis increase (Glycogen to glucose)

- Gluconeogenesis increase (Synthesis of glucose from fat)
- Glycolysis decrease (glucose utilization)

Somatomedins 00:18:15

IGF-1 = somatomedinc

↓

Major form / peaks during puberty

secretion depends on GH

Promotes skeleton and cartilages growth of bone

IGF11 = MSA

- Multiplication stimulation activity
- It is major form of somatomedin in fetus. (For fetal growth)

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Note

GH decrease = Dwarfism

GH normal → Receptor mutated → Laron Dwarfism

GH increase

Before closure of epiphysis

↓

Gigantism

After closure of epiphysis

↓

Acromegaly

1. Increase hand / foot size
2. Increase size of mandible (prognathism)
3. Increase heel pad thickness

4. Coronary heart disease
5. Hypertension
6. Carpel tunnel syndrome
7. Sleep apnoea

Treatment

- Trans-sphenoidal surgical removal of microadenoma
- Somatostatin analogue – octreotide, lanriotide
- GH receptor antagonist – pegvisomant

Hormone responsible for fetal growth 00:25:50

- Insulin → it increases cellular uptake of glucose
- IGF
- Thyroid hormone
- Glucocorticoids
- Leptin

GH has no role till 36 weeks

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Prolactin 00:27:02

Increase prolactin	Decrease prolactin
• Maximum: during pregnancy lactation and suckling • Sleep (REM) • Stress • Exercise	Dopamine agonist (bromocriptine)

- Hypoglycemia
- Dopamine antagonist
- Sexual intercourse

Action of prolactin hormone

- Lactogenesis stimulate milk production
- Increase size of breast (Mamogenesis)
- Decrease ovulation
- Decrease spermatogenesis
- Decrease sex drive / libido

THYROID GLAND

- Largest endocrine gland
- Weight: - 10-20 grams
- Location: - below larynx/either side of anterior trachea
- Right lobe – more vascular

  -Enlargement is common
- Left lobe → abscess formation more in left lobe since less vascular
- Isthmus

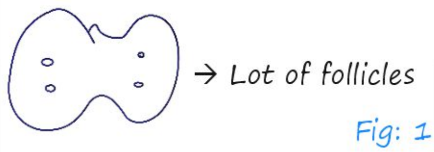

Fig: 1

- 2 types of cells

  i. Follicular cell → precursor for thyroglobulin

  ↓

  Tyrosine

  ii. Parafollicular cells

  ↓

  Also called as C cells → release calcitonin

  ↓

  Stain less /clear cells
- Embryologically, they migrate from base of the tongue to cover second and third tracheal ring

  ↓

  Primitive descent pathway → thyroglossal duct
- It there is failure to descent – lingual thyroid

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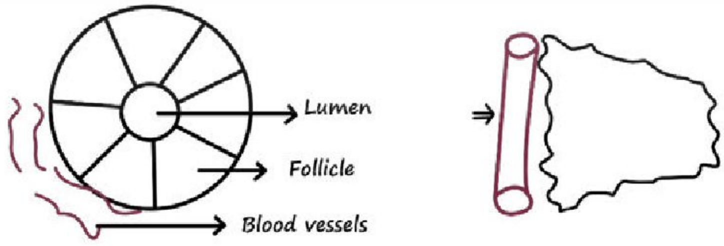


Fig: 2

- Follicle has TSH receptor to stimulate thyroid hormone ← increase CAMP
- iodide trapping occurs via Na-I symport
- this Iodide is thrown inside by pendrin protein
- mutation of pendrin protein- pendred syndrome

  ↓

  Clinical feature – goitre & SNHL

- This iodide is converted to iodine by thyroid peroxidase (TPO)
- Control of sodium Iodide – iodine trapping (rate limiting step)
- Na-I symport present in
  - Thyroid gland
  - Salivary gland
  - Gastric mucosa
  - Placenta
  - Choroid plexus

Autoregulatory method

- Perchlorate, pertechnate, thiocyanate → can interfere with iodine (compete with sodium)
  1. Oxidation of Iodide → Iodine (→ needs TP)
  2. Organification of Iodine (TPO + H_2O_2)
     - Lumen will have thyroglobulin
       ↓
       Back bone of tyrosine
     - Iodide will attach to thyroglobulin either 1 or 2

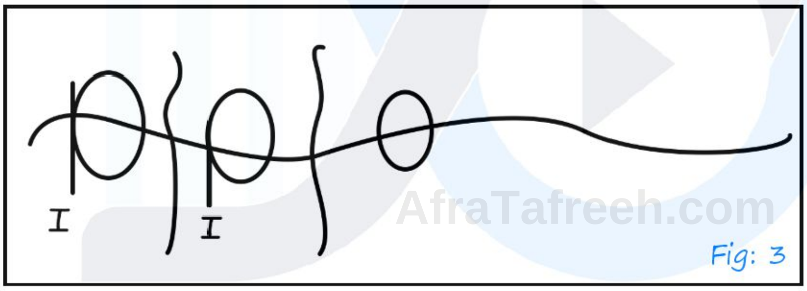


Fig: 3

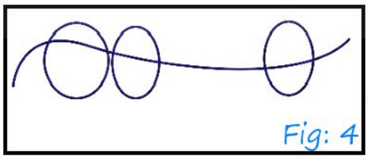
     - When lumen is cut → non thyroxin/DIT
  3. Coupling – under influence of TPO
     - DIT + DIT = T4
     - MIT + DIT = T3
     - DIT + MIT = rT3
     -  = rT3

Fig: 4

  4. Antithyroid drug like propylthiouracil/methimazole/carbimazole inhibit TPO

Release of T4 and T3/rT3

- Thyroglobulin reabsorbed by follicular cell by process of endocytosis
  ↓
  Phagolysosome
- Blood can have T3, T4

- T3 has 15-fold more affinity than T4 for thyroid receptor
- T3 → enter in the nucleus → bind with thyroid receptor
- Thyroid receptor – α – heart / muscle
  - β – pituitary
- Thyroid hormone combines with thyroid receptor and forms heterodimer with RXR

↓

Act on thyroid hormone response element

Expression of gene | Suppression of gene

↓

Promotor region of target gene

- Thyroid resistance is more common for β
- T3 and T4(70%) bind with thyroid binding globulin (plasma protein)
- Remaining T3 binds with albumin
- Remaining T4 binds with pre-albumin or transthyretin

↓

Precursor

- T4 - prohormone
  (t half – 7 days) → biologically inactive
  → happens in liver, kidney

↓

T3 (active form) | γ T3

- T4 converted to T3/ γ T3 by Deiodinase 1and 3
- D2 → acts on OUTER ring deiodinase → MIT & DIT
- D3→ acts on inner ring deiodinase
- D1→ acts on outer and inner ring
- During thyrotoxicosis, D1 is the main hormone
- D2 is N→ physiological
- Propylthiouracil → acts on D1
  → good drug in thyrotoxicosis
- TSH → works on thyroid gland
  → accumulates particular cells

Actions of TSH

- Iodide uptake
- Colloidal endocytosis

- Growth of gland
- Upregulated by TRH
  - TRH → TSH → T3T4

    +
- Downregulated by T3/T4
- In abese persons → leptin causes increase TRH

  ↓

  Increase TSH

TRH

- TRH activates
  - TSH
  - Prolactin
- Dopamine inhibits
  - prolactin
  - TSH
- i.e., why dopamine blockers → activates prolactin and TSH
- 3-20 mg of Iodine in thyroid gland
- RDA of Iodine – 150 mcg

70% | 30%

Catabolized 105 mcg | Goes to gland (45mcg)

+

45 mcg

150 mg → metabolized in urine

- Best way to check Iodine levels → urine
- Iodine levels → 50-100 mcg – mild Iodine deficiency
  - 20-50- mcg- moderated deficiency
  - < 20 mcg – sever Iodine deficiency
- Breast feeding/pregnancy → RDA of Iodine → 200-250 mg
  - In school children – 120 mcg
  - In preschool children – 90 mcg
- Suppose Iodine is very high

  ↓

  Blocked by Iodine trapping

  ↓

  Acute wolf chaikoff effect → hypothyroid

  ↓

  Excess iodine taken and blocking the mechanism of sodium Iodine symport

- After that → organification is affected

  ↓

  Chronic Wolff chaikoff effect

  ↓

  Hypothyroidism
- Excess Iodide causes failure of autoregulation

  ↓

  Hyperthyroid → JOD Basedows effect
- Colloid iodine
- Lugol iodine

} → used in – thyroid storm

–Pre-operative to surgery

Functions of thyroid hormone

- Increase BMR →increase Na potassium ATPase
- Can work on Brain → maturation
- Work on lungs → increase RR
- Work on Heart → permissive action on catecholamine increase HR/increase CO/increase SU
- Menstrual cycle disturbed

Tests

- T3
- T4

} → influenced by plasma proteins

- Always FT3/FT4 measured

  ↓ ↓

  (0.3%)/ (0.03%
- Main test in always TSH
  - T3 decrees with age
  - Obesity → increase leptin increases TSH

Increase TSH	Decrease TSH
• Dopamine antagonist – Metoclopromide – Amphetamine – Clomiphene	• Dopamine agonists – Bromocriptine – Dopamine – glucocorticoid – growth hormone – Metfomin

- Propranolol decrease conversion of T4-T3

  (Not by metoprolol atenolol)

- Amiodarone - contains 35% of Iodine
  - Hypothyroidism
    - ↓ Continue drug + Treat thyroid
  - Hyperthyroidism
    - AIT-I ↓ Give anti thyroid drug
    - AIT -II ↓ give steroids (due to destruction of gland)

- AIT→ amiodarone induced thyrotoxicosis
- Amiodarone masts β receptors → thyrotoxicosis will be asymptomatic
  - Lithium → 50% develops goiter
    → cause hypothyroidism even years later of taking drug
  - Sunitinib → RTK1
  - Interferon α
  - Cytokines

Sick Euthyroid Syndrome 00:47:10

- Patient is in ICU → mediated by cytokines
- Mild to moderate illness → T3 decrease
  → FT3 decrease
  → rT3 increase

↓

Purpose is to conserve calorie

↓

Active, form decrease

↓

Inactive form increase

↓

Sick euthyroid

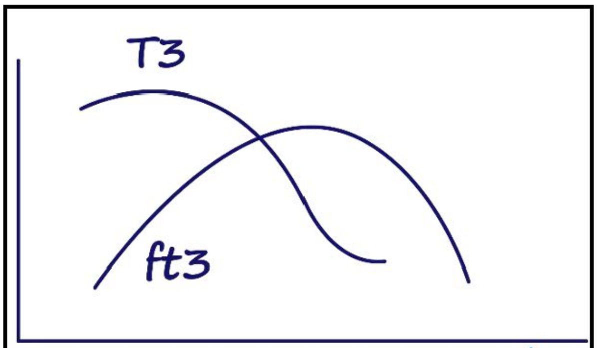


Fig: 5

- Sever illness → T3 decrease
  → ft3 decrease
  → T4 decrease
- TSH = N/decrease – initial
- TSH increase → . Recovering

TSH increase

- T4 increase → TSH adenoma
- T4 N → subclinical Hypothyroid
- T4 decrease → 1^{o} Hypothyroidism

TSH N

- T4 increase → estrogen
- T4 N → N
- T4 decrease → 2^{o} hypothyroidisms
  - Pituitary
  - Hypothalamus

TSH low

- T4 increase → thyrotoxicosis
- T4 N → subclinical thyrotoxicosis
- T4 decrease → 2^{o} hypothyroidisms
  - Pituitary
  - Hypothalamus

- Some antibodies are also formed like
  - Anti-thyroglobulin antibody
  - TPO antibody
  - TRab (TSH receptor antibody)
    ↓
    95-99% graves' disease
- TPO → Hashimoto's but not exclusive
- Calcitonin → useful foe making diagnose of medullary thyroid cancer

Symptoms (Hypothyroid)

- Tiredness/depression/impaired memory/myxedema madness/peripheral nerve compression → carpal tunnel syndrome
  ↓
  Slow DTR → hung up reflex

- GIT → enlarged tongue
  - → dysphagia
  - → slow intestinal movement
  - → achlorhydria – atrophy of gastric mucosa
  - → malabsorption → myxoedemous inflammation of bower wall
- Musculoskeletal → arthralgia
  - → stiffness of joint
  - → cramps
- Skin → swelling
  - → dry
  - → cool/pale
  - → itching
  - → dry hair/hair loss
  - → sparse eye brow laterally
  - → brittle nails
- Heart → decrease HR
  - → diastolic HTN- increase TRP
  - → narrow pulse pressure
  - → decrease CO
- RS → hypoventilation
  - → pleural effusion
- Metabolic → decrease Na
  - → decrease glucose
  - → increase uricemia
  - →increase LDL
- Ovulation → anovulatory /infertility

  ↓

  Due to hyper prolactin
- Non pitting edema due to deposition of hyaluronic acid in dermi's
- Hygroscopic nature → weight gain
  - → swelling
  - → voice change
  - → coarse features

TUTORIALS
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Management

- Levothyroxine 1.6 mcg/kg body weight
  ↓
  Absorbed in acidic pH
- Extreme form of hypothyroidism
  - increases TSH
  - Decrease T3

  ↓

  → Myxedema coma

  → Increase mortality

  → Presents with
  - Hypo thermia
  - Hyponatremia
  - decrease BP
  - decrease glucose
  - hypoventilation

  i.v inj of levothyroxine 300 mg
- infection w/o fever

ADRENAL GLAND

Adrenal gland

Cortex 72% | Medulla 28%

- Zona glomerulosa (15%)
  - Ovoid cells
  - Release mineralocorticoid (Aldosterone)
  - not under control of ACTH
- Zona fasciculata (50%)
  - Has fascicles / bundles
  - Release glucocorticoid (Cortisol)
- Zona reticularis (7%)
  - Like mesh / network
  - Release androgen

DHEA
↓
Testosterone
↓
Estrogen in females

Note

- In panhypopituitarism, aldosterone release is not affected. Because It is not under control of pituitary
- Most potent stimulus increase K^+ >> Hypovolemia > Hyponatremia

- Zona glomerulosa can regenerate, zona fasciculata and zona reticularis
  - G – Aldosterone → salt
  - F – Cortisol → sugar
  - R – DHEA/T → sex

(Stress / fever / decrease glucose / decrease BP) ⊕ (Stimulants)

$$\begin{tikzcd}
\text{CRH (Gs)} \arrow[d, "\oplus"] \\
\text{ACTH} \arrow[d, "\oplus"] \\
\text{Cortisol} \arrow[uu, bend right, "\oplus"']
\end{tikzcd}$$

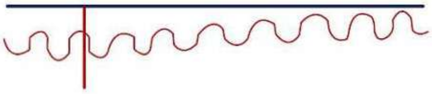
Circadian rhythm

ACTH – Max: early morning
Min: Night

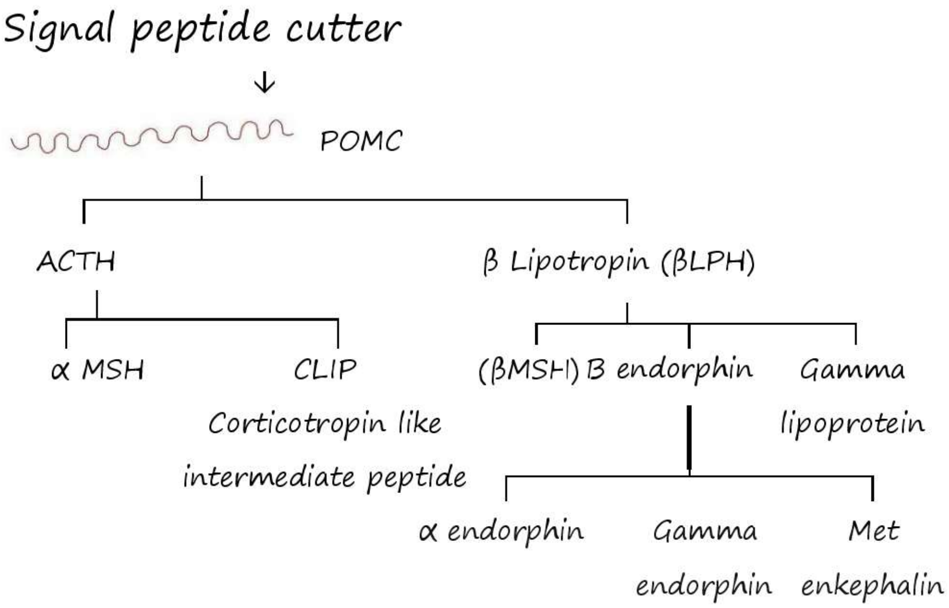
Stimulants

i. CRH
ii. Vasopressin
iii. IL-6
iv. Leukaemia Inhibiting factor

CRH
Pre ↓ POMC
POMC / Preopiomelanocortin



(Pre – POMC)


Signal peptide cutter
POMC
ACTH
β Lipotropin (βLPH)
α MSH
CLIP
Corticotropin like intermediate peptide
(βMSH) B endorphin
Gamma lipoprotein
α endorphin
Gamma endorphin
Met enkephalin

Inhibited

i. Glucocorticoids

ACTH 00:13:40

Act on melanocorticotropin receptor 2 (MCR-2)

1.Import cholesterol esters into adrenal cortex

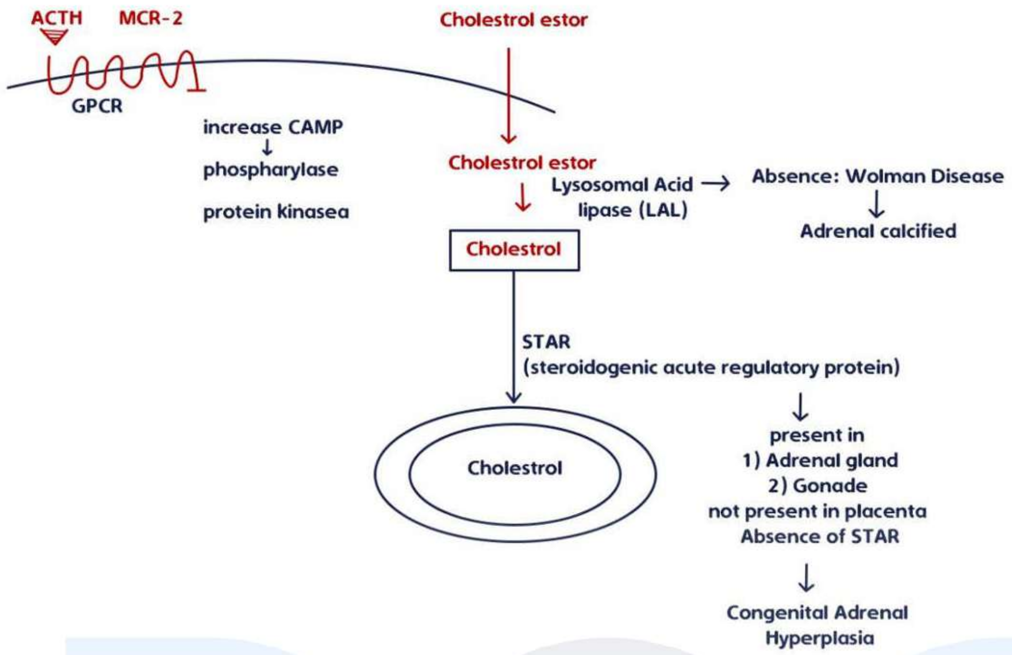
2.Cleave cholesterol esters into cholesterol for import into mitochondria

3.Cause increase in transcription of various enzymes

- It can stimulate only MCR-1 if it is in high doses
- It is generally stimulated by α MSH

Physiologally – $\text{ACTH} \xrightarrow[\text{Stimulate}]{} \text{MCR-2}$

$\text{MCR } 1,3,4,5 \xrightarrow[\text{Stimulated by}]{} \alpha_1\ \beta_1\ \gamma \text{ MSH}$


ACTH
MCR-2
GPCR
increase CAMP
phospharylase
protein kinasea
Cholestrol estor
Cholestrol estor
Lysosomal Acid lipase (LAL)
Absence: Wolman Disease
Adrenal calcified
Cholestrol
STAR (steroidogenic acute regulatory protein)
present in
1) Adrenal gland
2) Gonade
not present in placenta
Absence of STAR
Congenital Adrenal Hyperplasia
Cholestrol

cholesterol ester

Cortisol 00:22:35

- Cortisol is 1000 time more than mineralocorticoids
- Cortisol has equal affinity to mineralocorticoid receptors

↓

But it does not act on principle cell of collecting duct, because it is inhibited by 11 β hydroxy steroid dehydrogenase

- But in cushings disease (i.e excess cortisol) it acts on mineralocorticoid receptor leading to Na^+ absorption hypertension, edema

Functions

1.Hyperglycemic hormone (adrenal diabetes)

2.Catabolic to protein

3.Lipolytic – mobilize fat towards centre

↓

- Centripetal obesity
- Buffalo hump
- Thinning of skin

4.Suppress immunity by inhibiting phospholipase A_2

5.Decrease eosinophils, lymphocyte, basophils

6.Increase neutrophil, platelet, monocytes, red blood cells

7.Permissive role

Act like catecholamine eg lipolysis, Bronchodilation, pressor response etc.)

+

Calorigenic action of glucagon

8.CNS → Alter mood and behaviour / increase appetite

9.CVS →increase cardiac output / increase peripheral vascular tone

10. Kidney → increase GFR, increase excretion of calcium. decrease ADH

11. Bone → increase bone resorption by activating osteoclast

12. GIT →

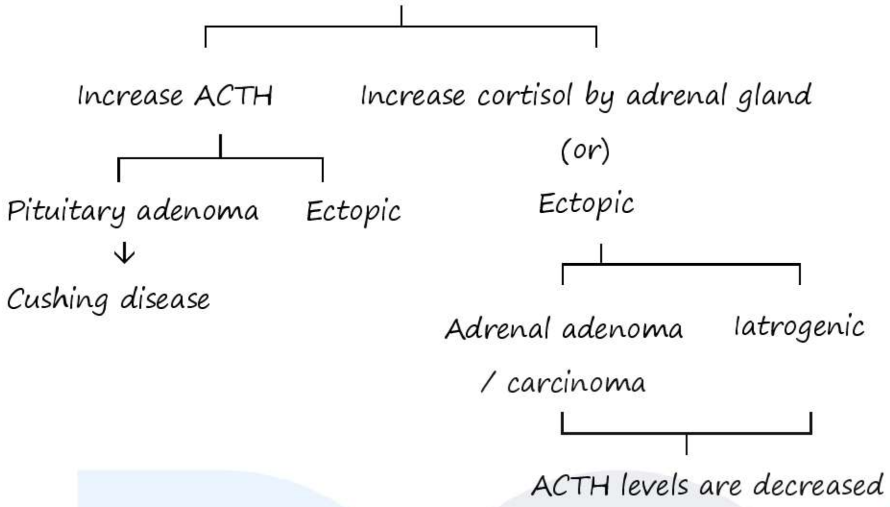
- It increases gastric acid secretion
- It decreases calcium absorption
- It increases GI mucosal epithelial cell proliferation

13. Reproductive system: decrease GnRH

AfraTafreeh.com TUTORIALS LOGIN FOR SUCCESS

Cushing syndrome 00:33:00

- It is due to excess of cortisol


Increase ACTH
Increase cortisol by adrenal gland
(or)
Ectopic
Pituitary adenoma
Ectopic
Cushing disease
Adrenal adenoma / carcinoma
Iatrogenic
ACTH levels are decreased

Features

1. Centripetal obesity
2. Thin hair
3. Moon face
4. Osteoporosis
5. Hypertension
6. Psychosis
7. Cataract
8. Peptic ulcer
9. Increase glucose
10. Menstrual disturbance
11. Myopathy
12. Thinning of skin / purple striae
13. Pigmentation (High ACTH)

Addison disease 00:39:15

- Autoimmune / Tb / carcinoma / HIV / surgical removal

Decrease Cortisol
Increase ACTH: - seen

Decrease Aldosterone

Decrease Sex Corticoids

Congenital adrenal hyperplasia 00:40:33

- mnemonic – if numerical is 1 it will increase
  anything other than 1 it will decrease

	BP	testosterone
21 hydroxylase deficiency	decrease	increase
11 β hydroxylase deficiency	increase	increase
17 hydroxylase deficiency	increase	decrease

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21 Hydroxylase deficiency (>90% cases)

BP decreased: Aldosterone deficiency → Hyponatremia
Hyperkalemia
since, cortisol less:
Hypoglycemia
{ACTH is high}

Testosterone increase
↓
♀: Virulisation
Clitoromegaly
Increase facial hair
Deep voice
Increase libido
Irregular menstrual cycle

Diagnosis

- increase 17 hydroxy progesterone – best test
- others
  - androgens increase
  - aldosterone decrease
  - cortisol decrease

Treatment

- supplement
  - cortisol
  - aldosterone

11 β Hydroxylase deficiency (5 to 8%)

- second most common
- increase BP → Hypertension / fluid retention / decrease renin / increase testosterone

17 α hydroxylase deficiency

- BP increase
- Testosterone decrease

  ↓

  ♂ have female like genitalia

ENDOCRINE PANCREAS

- It constitutes 1-2 million islets of Langerhans
- These are maximum in tail of pancreas

α cells → Present in periphery

β cells → Are located in center

γ cells → Diffusely distributed

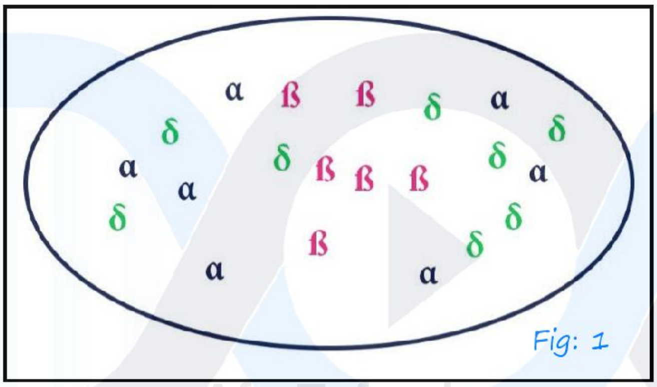


Fig: 1

Hormones secreted

β cells → Insulin, C – peptide, Amylin

α cells → Glucagon

delta cells → Somatostatin

F cell/PP → Pancreatic polypeptide

Epsilon → Ghrelin

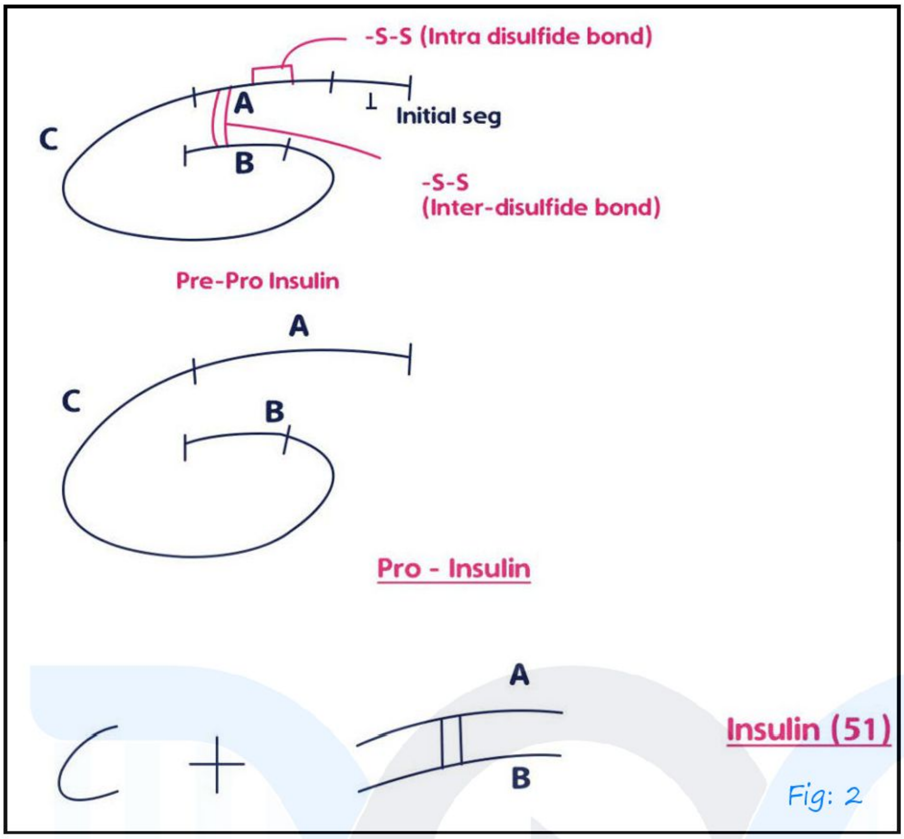

-S-S (Intra disulfide bond)
A
Initial seg
C
B
-S-S
(Inter-disulfide bond)
Pre-Pro Insulin
A
C
B
Pro - Insulin
A
B
Insulin (51)

Fig: 2

Zinc stabilizes Hexameric structure of insulin

Amylin → Also known as islet amyloid peptide

it slows down rate of appearance of glucose in blood

↓

- It decreases glucagon secretion
- It delays gastric emptying
- And thus, it decreases food intake

Synthetic amylin analogue: Pramlintide – given subcutaneously

Release of insulin from β cell 00:08:02

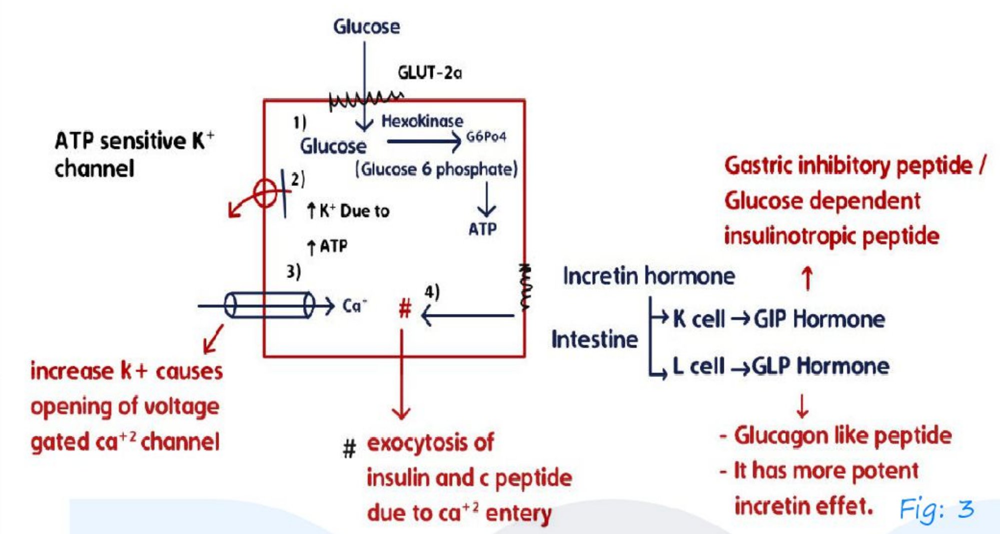

Glucose
GLUT-2a
1)
Hexokinase
Glucose
G6Po4
(Glucose 6 phosphate)
ATP sensitive K⁺ channel
2)
↑K⁺ Due to
↑ATP
ATP
3)
Ca⁻
#
4)
Incretin hormone
Intestine
K cell → GIP Hormone
L cell → GLP Hormone
Gastric inhibitory peptide / Glucose dependent insulinotropic peptide
increase k+ causes opening of voltage gated ca⁺² channel
# exocytosis of insulin and c peptide due to ca⁺² entery
- Glucagon like peptide
- It has more potent incretin effet.

Fig: 3

Note

- **Sulphonylureas** → Act on ATP sensitive K^+

  Example: Glimeperide
  Gliclezide
  Glibenclamide
  ↓
  They have hypoglycemia + wt gain as side effects

- **P – 1 agonist:** Subcutaneous injection

  Example: exenetide
  Liraglutide

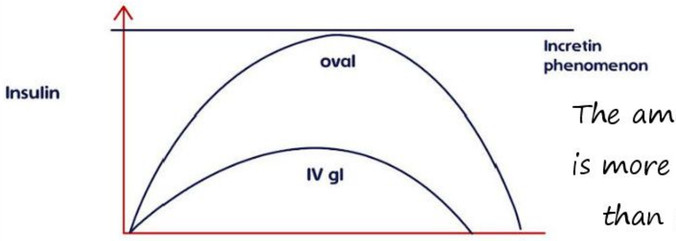
  Advantage: decrease body weight

They are degraded by DPP-4, therefore DPP4 inhibitors increase action of GLP-1 agonist

↓

Eg: Sitagliptin
Linagliptin → only drug can be given in renal disease
Veldagliptin
Sexagliptin

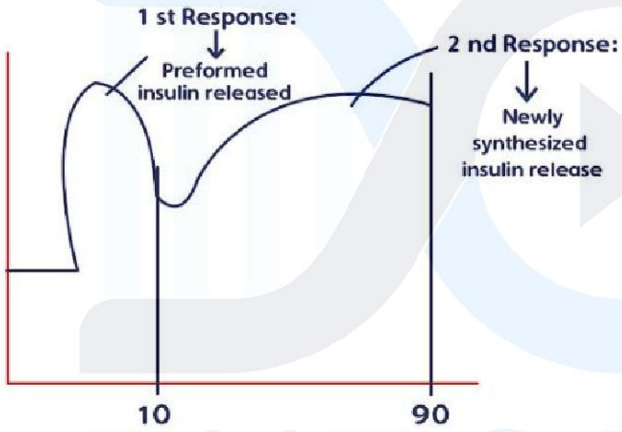
Incretin effect



The amount of insulin released is more on oral administration than on IV administration

Fig: 4

Biphasic insulin release



1st Response: Preformed insulin released

2nd Response: Newly synthesized insulin release

Fig: 5

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Somogyi phenomenon	Dawn phenomenon
Increase insulin administration	Decrease insulin administration
At night causes → hypoglycemia ↓ Reactive hyperglycemia	Hyperglycemia
At early morning: due to GH	Hyperglycemia
Therefore management – decrease insulin dosage	Management = increase insulin dosage

Both phenomenon can be differentiated by measuring glucose levels at night.

Functions of insulin 00:21:20

- Insulin act on tyrosine kinase receptor

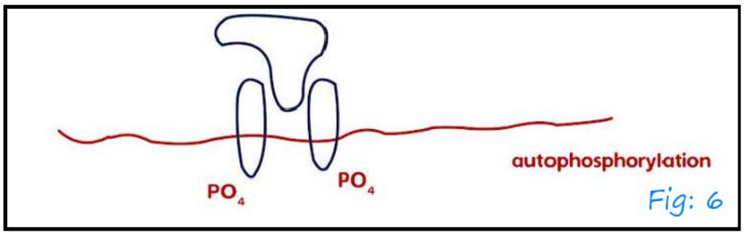


Fig: 6

↓

Insulin receptor substrate

MAP Kinase (Mitogen activated protein kinase)
↓
mitosis
↓
cell growth

P13 kinase pathway
↓
metabolic function
↓
1. It act on GUT4 → Muscle and fat
↓
Mobilization of GLUT4 to periphery occurs so that glucose can enter
↓
thus, causing hypoglycemia

2. Insulin causes influx of K^+ into cell → Hypokalemia

3. All metabolic pathways causing hypoglycemia will be activated

E.g.: Decrease Glycogenolysis
Increase Glycogenesis
Decrease Gluconeogenesis

HbA1c 00:27:56

- It is glycosylated hemoglobin (gives average glucose concentration of 3-4 months)
- Normally <5.7 in non-diabetics

Target HbA1c: 6.5 ⟶ 8

6.5 ↓

Tight control
- Young age
- Increase life expectancy
- No comorbidities
- Recent onset

8 ↓

- Old age
- Many comorbidities
- Long H/O DM

Diagnosis of DM

	Normal	**Prediabetic**	**Diabetes**
Fasting	<100 mg/dl	100-126	>126
2hr OGTT	140 mg/dl	140-199	>200
Hb A_1 C	<5.7	5.7-6.4	>6.5

Symptoms

- Polyuria
- Polydipsia
- Polyphagia

Types of Diabetes

1.Type 1 DM

- <25 years / thin
- Autoimmune diabetes due to β cell destruction
- It is less common
- Autoantibodies formed against

  i. GAD (Glutamic Acid Decarboxylase) → most common

  ii. Insulin cell antigen – Anti insulin antigen

2.Type 2 DM

- It is multifactorial (Genetic, Environmental), Life style V3 activity & food
- Insulin resistance is most common finding: Normal concentrations of insulin causing subnormal action
- Increase visceral & abdominal fat– increase concentration of FFA

↓

Cause serine / threonine phosphorylation of IRS (Insulin Receptor Substrate)

↓

Insulin resistance

3.1.5 / Type 3 DM

- It is a variety of Type 1 diabetes
- Slowly progressive destruction of β cells seen

4.Maturity onset diabetes of young (Mody)

- It is a variety of type 2 presenting early in age

- MODY 1: Mutation of HNF 4 α
- MODY 2: Gluco kinase mutation
- MODY 3: HFF 1 α Mutation (most common)
- MODY 4: IPF - 1
- MODY 5: HNF 1β
- MODY 6: NDI

5.Pancreatic defect

- Cystic fibrosis
- Hemochromatosis
- Chronic pancreatitis

6.Endocrinopathies

Mnemonic CHAP G>

- C: Cushing Disease: Adrenal Diabetes
- H: Hyperthyroid: Thyroid Diabetes
- A: Acromegaly: Pituitary Diabetes
- P: Phaeochromocytoma
- G: Glucagonoma

7.Infections: Measles / Mumps / Cox sackie

Complications 00:41:00

Type I	Type II
• DKA lipolysis occurs only in complete absence of insulin leading to production of ketone bodies (β hydroxybutyrate and Acetoacetate) ↓ Metabolic acidosis sugar levels: 250-600 **clinical features:** • Thirst /nausea • Abdominal pain • Increase R.R – Kussmaul breathing → to compensate metabolic acidosis	• Hyperosmolar hyperglycemic state (HHS) • No lipolysis therefore no ketone bodies • Insulin decrease and increase counter regulatory hormones increase blood glucose levels seen (600-1200 mg/dl) ↓ osmotic diuresis and severe dehydration ↓ COMA / Death • Mortality HHS > DKA **Triad** • Hyperglycemia • Increase osmolarity (330-380) • Dehydration

DOT TUTORIALS LOGIN FOR SUCCESS

CALCIUM HOMEOSTASIS

- 3 hormones important for calcium
  - Parathormone → increase Ca/decrease Po4
  - Vitamin d3/calcitriol → increase Ca/increase Po4
  - Calcitonin → (decrease Ca)
- Hyperparathyroidism – High calcium
  - Low phosphate
- Hypoparathyroidism – low calcium
  - High phosphate
- Hypervitaminosis D3 – High calcium
  - High phosphate
- Rickets/osteomalacia – low calcium
  - Low phosphate

Normal value of calcium

- 10 mg/dL 5meq/L /2.5 mmol/L

Calcium

- 50% free/ionized
  - Physiological active form ↓
    - Secondary messenger
    - Blood coagulation
    - Muscle contraction
    - Exocytosis
    - Nerve function
- 9% complexed to anion
  - Citrate
  - Phosphate
  - HCO_3
- 41% protein bound
  - Albumin
    - Non diffusible
    - 1g/dL increase albumin
    - Increase Ca by 0.8mg/dL
  - globulin

Increase pH/alkalosis = decrease Ca- tetany

- Proteins are abundant buffer in the body

  ↓

  Can bind to protons also and calcium also

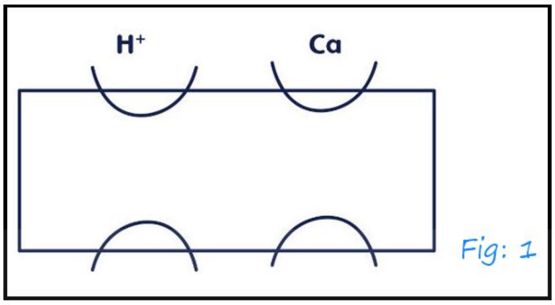


Fig: 1

- Metabolic alkalosis → protons are less

  → size availability of Ca increase

  ↓

  Decrease free calcium level

Decrease pH/acidosis= increase Ca → Hypercalcemia

- Ca absorption – Duodenum/proximal jejunum
- Ca absorption facilitated by Gastric acid
  Proteins in food
- Ca absorption inhibited by – Phytates
  - Phosphates
  - Oxalates

Tetany 00:12:41

- Decrease Ca
- Neuromuscular irritability /increase excitability
- Causes: – Hypocalcemia

  - Hypomagnesemia
  - Alkalosis

- Calcium stabilizes membrane → flow

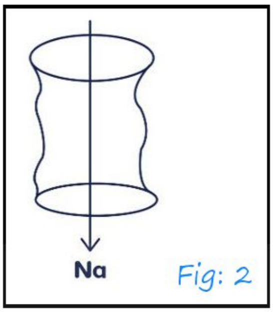


Fig: 2

- Voltage gated sodium channel is important for depolarization of action potential
- Voltage gated sodium channels are guarded by calcium ion

↓

Repel extra Na

- Decrease Ca → guarding decrease

↓

Entry of sodium increase

↓

Depolarization

↓

Increase excitability

- ↓↓↓ Mg→ Gittlemann syndrome- mutation of Nacl in DCT

↓

Tetany

↓

- Severe decrease in magnesium cause Decreases PTH release

↓

Decrease free calcium

TUTORIALS LOGIN FOR SUCCESS

- 2 signs i. Chvostek sign 8% in other conditions

  ii. Trousseau sign → more specific 1%

Chvostek sign

- If your tap facial nerve there will be contraction of facial muscles

Trousseau sign

- Carpopedal spasm precipitated after ischemia

  ↓

- BP, cuff inflated for 3 minutes

Clinical symptoms

- Mild hypocalcemia
  - Circumoral numbness
  - Muscle cramps
  - Paresthesia (Tingling) — Hand, Feet

Severe

- Seizures
- Laryngospasm
- Myocardial infarction

EMG

- Spontaneous discharge from motor unit in the form of multiple motor unit

Treatment

- Calcium gluconate
- Calcitriol
- Na channel Blockers

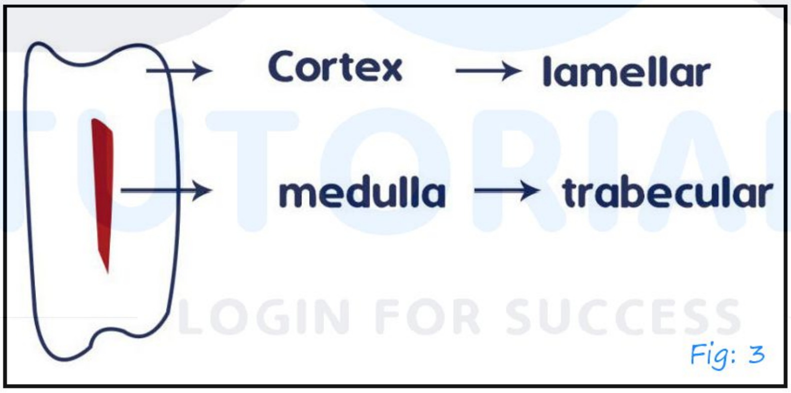
Cerebral tetany

- Generalized tetany without loss of consciousness /tongue bite, post ictal confusion
- Anticonvulsant should no be given

  ↓

  D3 catabolized → ↑↑ symptoms

Bone 00:25:58


Cortex → lamellar
medulla → trabecular
Fig: 3

- Minerals – Hydroxyapatite
  - – Type I collagens
  - – Chondroitin sulphate
  - – Osteo calcin
  - – Osteo nectin

- Bone forming cell → osteoblast

  ↓

  Derived from cells of mesenchymal origin

- Secrete organic matrix and aids in mineralization
- Transcription factors needed are
  - RUNX2
  - BMP
  - INH
- Mutation of RUNX2 – cleidocranial dysplasia
- Osteocytes → osteoblasts after embedding

  ↓

  Osteocytes

  → Communicating with osteoblast via canaliculi

  → Most abundant cells in bone

  → Major source of fibroblast growth factor 23

  ↓

  Regulate PO4

- SOST → sclerostin → Inhibit differentiation of osteoblast

↓

Mechanosensory i.e., inhibit bone formation

Mutation

↓

Excessive bone formation

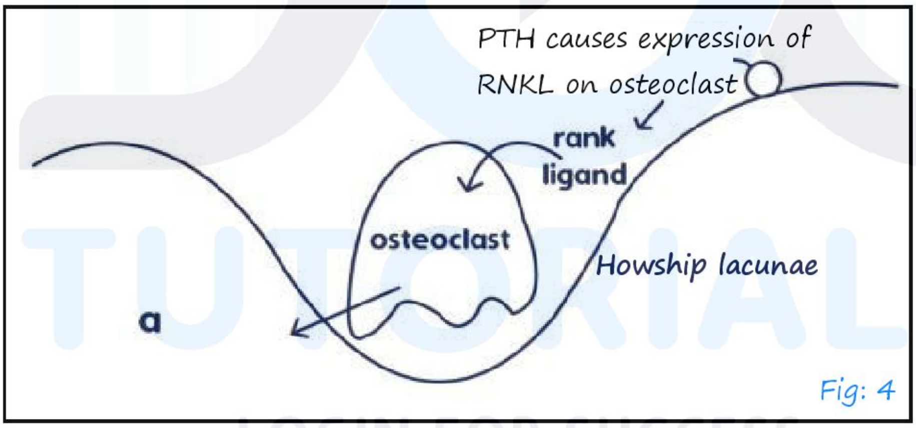
↓

Sclerosteosis

Osteoclast

- Bone resorption cell
- Derived from hematopoietic lineage

  (Different from osteoblasts)



PTH causes expression of RNKL on osteoclast

Fig: 4

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- PTH and vitamin D3 have receptors on osteoblast cell

↓

Activate a ligand called RANk ligand

↓

Activated osteoclasts

(Definite shape to bone)

- Osteoclasts work only in acidic environment

↓

For that need H+ pumps

↓

Carbonic Anhydrase II is needed

↓

$H_2O + CO_2$ – H^+ → cause acid

– HCO_3^-

- Protease → cathepsin – k –→ act # low pH

↓

Mutation → Pyknodysostosis

- To limit the function of RANK ligand

↓

Osteoproteogenin is needed

↓

Stimulated by Estrogen

– Testosterone

– Growth hormone

- In post-menopausal women → Estrogen decrease

↓

Post-menopausal osteoporosis

- DOC for osteoporosis – Bisphosphonates

↓

– Inhibitor of osteoclasts

– Increase bone density

– Drugs → alendronate

→ Ibandronate

→ Zolen chromate

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- Inhibit FFPS (Farnesyl pyrophosphate synthase)

↓

Mevalonate pathway

↓

Important for osteoclast survival

- Adverse effect:

Esophagitis → prevented

↓

→ empty stomach

→ lot of water

→ should not lie down for 1 hr.

Denosumab

- Monoclonal antibody against Rank ligand
- Given for postmenopausal women
- Strontium Raneolate → increase Bone formation
  ↓ resorption
  → given for osteoporosis
- SERM – tamoxifen

Parathyroid gland 00:51:06

- 3rd pharyngeal pouch – inferior para thyroid gland
- 4th pharyngeal pouch – superior parathyroid gland
- 2 types of cells

Chief cell
↓
Most abundant
↓
PTH
↓
Sulphur amino acid

Oxyphilic cell
↓
Large cell – less abundant
↓
Increase mitochondria

PTH increased by: –

- Decrease Ca
- Decrease Mg (mild decrease)
- Hyperphosphatemia
- Catecholamines

PTH decrease by: –

- Increase Ca/D3
- ↓↓↓ Mg (Gettleman syndrome)
- Combined decrease in Ca and Mg

Calcium sensory receptor

- PTH gland
- Calcitonin producing C- cells
- Renal tubule
- Brian

} serpentine receptors

Mutation of calcium sensory receptors

↓
AD
↓
FHH (Familial Hypercalcemic Hypocalciuria)
↓↓
→ ↑↑ Ca
→ ↑↑↑ PTH

} Hyper parathyroidism
↓
Increase PTH
Increase Ca
↓
Sx

↓
counselling

Family history

PTH not that high

PTH receptors

- Mainly 3 types

PTH1/PTH r
PR
↓
Can bind to
PTH e PTHrP
↓
Present in Bone,
kidney
↓
Not in intestine
↓
Synthetic PTH
for osteoporosis
↓
Teriparatide

PTH2
↓
Can only bind
with PTH
↓
Present in
Brain, placenta,
pancreas

e PTH rec
↓
Binds to
carboxy
terminal of
PTH
↓
Binds to
bone

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- Mutation of PTH receptors - jansen disease

Action of PTH @ different level

- Bone → PTH activate osteoblast
  ↓
  Activates osteoclasts
  ↓
  Activates RNAK-L

- Kidney → increase calcium resorption from DCT

↓ PO4 resorption (PCT)

→ activating conversion of 25 OH CC)

↓ 1 hydroxy PTH

1,25 (OH) CC

- In kidney disease – give 1,25 (OH) CC
- In Hypoparathyroidism give 1,25 (OH) CC

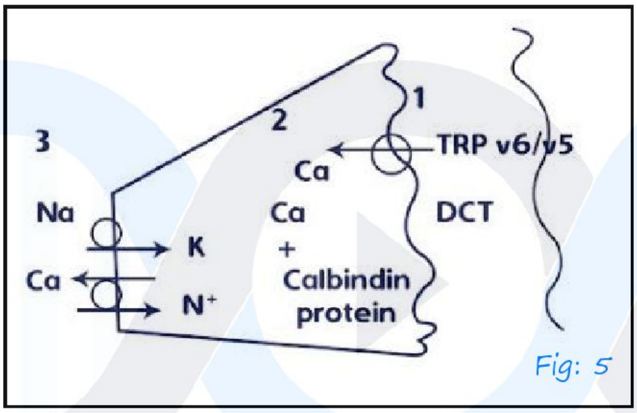

Fig: 5

- PTH acts on TPV6 /Vs which helps in calcium absorption
- In intestine → all 3 steps by vitamin D3 (PTH independent)

TUTORIALS LOGIN FOR SUCCESS

1° Hypoparathyroidisms	Pseudo hypo-parathyroidism	Pseudo pseudohypoparathyroidism
↓		
PTH decrease		
↓		
Ca decrease		
PO4 increase		
Phenotypic feature		
↓		

Shot 3rd and 4th
metacarpal
↓
Knuckle knuckle
dimple dimple sign
(KKDD)

Pseudo

- PTH receptor resistance
- PTH-N /increase
- Ca decrease
- Kinckle knuckle dimple dimple sign
- D.B 10 & pseudo hypo parathyroidism → injury PTH is given

If CAMP increase — If no change in CAMP

1° hypo — Pseudo

- Pseudo hypoparathyroidism and pseudo hypoparathyroidism features of Albright osteodystrophy syndrome

From mother
↓
Pseudo hypoparathyroidism
↓
All receptors are resistant
↓
PTN- N
Ca↓
KKDD sign +

From father
↓
Pseudo pseudohypoparathyroidism
↓
Only bone receptors not working
↓
PTH -N
Ca-N
Lab-N
KKDD sign +

Vitamin D3 01:16:55

- Formed from skin
- Has pro vitamin D(7 dehydrocholesterol)

↓ UV rays
Cholecalciferol
↓ Liver
25 (OH) CC- major circulating form

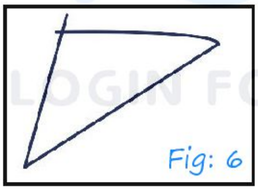

Fig: 6

PTH ↓ 1α hydroxylase
$1,25\ (OH)_2$ CC
↓
Supplemented in Hypoparathyroidism and CKD

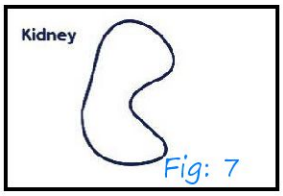

Fig: 7

- Status of D3 can be measured by 25 (OH) CC

Role of Vitamin D3

- Calcitriol → intestine → increase Ca
- Bone → similar to PTH → RANK l – oc

  ↑

  Increase Ca

  Increase PO4
- Kidney – increase Ca

  – Increase Po4

Calcitonin

- Decreases calcium and it is

  Synthesized and secreted by parafollicular C- cell

  ↓ ↓

  Clear

  Inhibit bone resorption

  decrease calcium absorption

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MALE REPRODUCTIVE SYSTEM

- On the short arm of chromosome Y → SRY gene

↓

Sex determining organ

↓

Has tesitis determing gene product

↓

Stimulate testis

Sertoli cell	Leydig cell
↓	↓
Secrete Mullerian inhibitory factor	Releases testosterones
↓	↓
Inhibits Mullerian system	Wolffian duct stimulation

- SRY gene → used for sex determination
- GnRH → released continuously

↓↓

Inhibit FSH / LH

- GnRH pulsatile action inhibited by
  - Melatonin
  - GABA

- What happens at puberty
  - There is a peptide called kiss peptide

↓

Acts on GnRH neuron

↓

Receptor → GPR 54

- Kiss peptide + GPR 54

  Necessary for pulsatile nature of GnRH
- Permissive role in achieving the puberty is leptin

- Leptin
  - Obtained from fat
  - Decreases hunger
  - To activate kisspeptin and GPR54

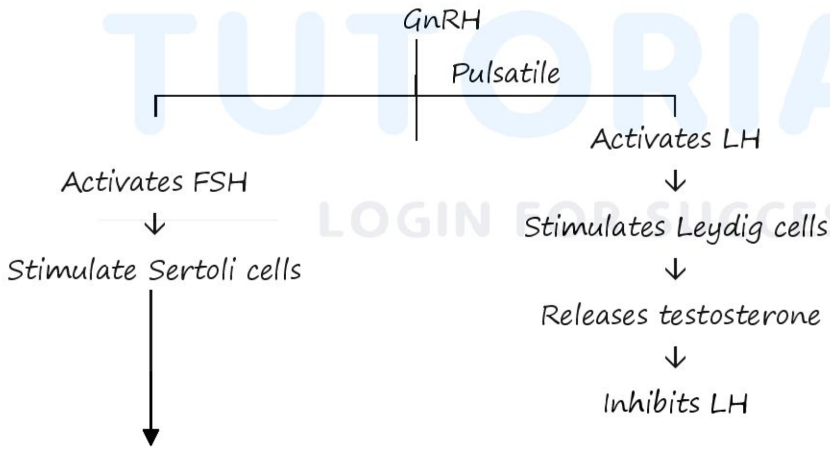
    ↓

    Pulsatile release of GnRH

Role of hormone control 00:08:48

GnRH → released from

- Arcuate nucleus
- Preoptic nucleus


GnRH
Pulsatile
Activates FSH
Stimulate Sertoli cells
Activates LH
Stimulates Leydig cells
Releases testosterone
Inhibits LH

1.Mulleran inhibitory substance

2.Inhibin → Inhibits FSH

3.Androgen binding protein

4.Formation of blood testis barrier

Testosterone

- After puberty:
  1.wolffian stimulation (internal differentiation → epididymis, vas deferens, seminal vesicle)
  2.Pubertal growth spurt, (axillary hair and pubertal hair)
  ↓
  In both male and female
  3.Deepening of voice
  4.Negative feedback of LH
- Testosterone is presence of 5 α reductase converted to dihydrotestosterone
  - Peaks during puberty
  - External genital organ, prostate growth

  In BPH → 5 α reductase inhibitor
  ↓
  Given for male pattern baldness

Spermatogenesis 00:15:09

- Occurs in seminiferous tubules → testis
- Lower temperature than body temperature is required
- Duration: - 74 days
- Hormones: - FSH, LH, TSH

  Even GH is needed for early division of spermatogonia

Stem cell
↓
Spermatogonia

Type A | Type B
↓ mitosis
1° spermatocyte (2N)
↓ Meiosis
2x2° Spermatocyte
↓
(2 spermatid) x 2
↓ → spermiogenesis
Mature sperm

spermiogenesis occurs in deep fold of cytoplasm of Sertoli cell

- Main hormone for spermiation → FSH
  Testosterone is also needed.

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Sertoli cell

- Also called as nurse cell
- Also form blood testis barrier
- Gives rise to MIS / ABP /
- Secrete aromatase to convert testosterone to estrogen
- Release inhibin

Changes in sperm when parsins through epididymis

- Spermatozoa acquire motility in epididymis due to activation of CATSPER → Ca^{2+} channel (12-26 days) → In tail of sperm

Capacitation and acrosome reaction

- Change in non-fertilizing to potential fertilizing sperm

↓

Start of cervix → completed in isthmus

Acrosome reaction

- Essential for zona binding and penetration by spermatozoa
- Occurs in ampulla of fallopian tube
- Fertilization occurs in ampulla of fallopian tube
- Sperm survives in female genital tract → 24-48 hours
- Vaginal secretion also aids in motility of sperm
- Semen → sperms + secretion of →

  1.60% of seminal vesicle

  2.30% prostate gland

  3.Cowper's gland

Seminal vesicle

- Provides nutrition for sperm
- Antioxidant like vitamin C
- Prostaglandins
- Phosphorylcholine → Used to defect seminal stain by Florence test

Prostate gland

- Releases fibrinolysin → cause liquification of semen
- Acid phosphatase because of prostate gland
- Spermin → barberio test

  Buffers like Hco_3 and Po_4^- → are available

FEMALE REPRODUCTIVE SYSTEM

Female sex hormone

- GnRH → Stimulate anterior pituitary hormones

follicle stimulating hormone (FSH)
↓
stimulates granulosa cell
↓
produce aromatase → C_{18} estrogen

LH
↓
act on theca cells
↓
produce androstenic

Menstrual cycle 00:02:35

Ovary

Endometrium

Cervix and vagina

Ovarian cycle

- 2 phases
  - Follicular phase (FSH)
  - Luteal phase (LH)
- Follicular phase → Growth of ovarian follicles under FSH

→ TSH stimulates ovarian follicle (15;20)
↓
Dominant ovarian follicle is called graffian follicle
↓
Have maximum FSH receptor and maximum aromatase

- Maximum estrogen is seen just before ovulation
- Increased FSH also help in lysis of follicle to release ovum
- Progressive increase in estrogen causes positive feedback mechanism → increase LH
- LH surge $\xrightarrow{\text{36 hours}}$ ovulation
- LH peak $\xrightarrow{\text{8 – 10-hour}}$ ovulation
- During ovulation body temperature increase 0.5 to 1°F
- After ovulation → Luteal phase start
- After ovulation → ovum enters fallopian tube, graffian follicle is filled with blood → Corpus hemorrhagicum

↓

Soon replaced by luteal cell

↓

Corpus luteum

↓

Forms progesterone (Pregnancy hormone)

- Corpus luteum(CL) waits for 10 days, if fertilization not occurred – CL degenerates
- If fertilization occurs, CL persists and secretes HCG
- Pain felt during ovulation → Mittelschmerz

Endometrium

- Changes

Proliferative Phase

↓

- Estrogen high
- Endometrial thickness increase
- Uterine gland enlarges (lengthen)

Secretary Phase

↓

- Max. thickness
- Uterine gland starts secreting clear fluid

Menstrual phase

↓

Separate 2/3rd of endometrium shed

↓

Spiral arteries under influence of prostaglandin

- Cervical mucosa becomes thin under Influence of estrogen

  ↓

  Smooth passage of sperm

  ↓

  Thinnest → ovulation happens

- Vaginal change
  - Under influence of estrogen → superficial cells
  - Under influence of progesterone → Intermediate cells

Hormones 00:16:40

- Steroid
  - Estrogen
  - Progesterone
- Protein
  - Inhibin B
  - Activin
  - Relaxin

- Inhibin B → decrease FSH level
- Activin → increase FSH
- Relaxin – Relaxes pubic symphysis and soften the cervix for delivery

Estrogen

- Estradiol E_2 – Prominent in menstruation (Pre menopause reproductive age)
- Estradiol E_3 – pregnancy
- During menopause – E1

Eg: C_{18}

- Uterus
- Kidney
- Heart
- Liver

α receptor

- Ovaries
- Prostate
- GIT
- CNS

β receptor

Role of estrogen

1.Uterus

- Increases sensitivity to oxytocin
- Makes excitable
- More contractile / more gap junctions

2.Breast → increase ductal growth of breast

3.Secondary sexual character / increase libido

4.Estrogen stimulate PG (Osteoprotogenin)

↓ ↓

Prevents osteoporosis inhibits Rank L

no Functing of osteoblast

5.Kidney will conserve more Na and H2o under influence of estrogen

Progesterone C_{21}

- Uterus
  - Anti-estrogenic (less excitable)
  - Less contractile
- Breast → Lobular growth
- CNS → Depressant action
- Thermogenic in nature → increase in temperature 0.5 to 1°F
- Increased Na and H_2o excretion – diuresis

GIT MOTILITY

- RMP of smooth muscle is not fixed. Keeps on fluctuating/Oscillating
- Fluctating RMP/Oscillatory RMP – Slow waves/Basic Electric rhythm → Generated by Pacemaker – Interstitial cell of CAJAL
- BER – Maximum in the duodenum → 12/min
- Minimum in the caecum → 2/min
- 2nd minimum in stomach → 4 /min
- BER cannot cause peristalsis/mechanical movement

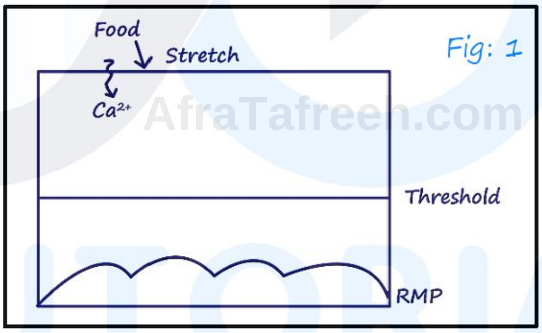

Fig: 1

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- When food taken → Acetylcholine is released and acts on muscarinic receptors (Gq) → Calcium enters cells
- Fluctation of RMP increases because of calcium influx
- Only when touches the threshold – Spike potential → Action potential
- Only when there is spike potential mechanical contraction can occur → Peristalsis & Migratory motor complex

- Electrical activity is converted into mechanical activity

Enteric nervous system 00:08:43

2types

Myentric plexus
↓
- Location is between inner circular layer and outer longitudinal layer
- Also called as auerbach plexus

↓
GIT motility

Ascending neuron
Descending neuron

Meisners plexus
↓
- Just below mucosa
- Submucosal plexus

↓
GI secretion

- 3types of motility

1.Peristalsis

2.MMC

3.Segmental movement

Peristalsis

- Lumen has bolus
- Below mucosa you have submucosal plexus

- Between outer longitudinal and inner circular cells

  → Myenteric/Auerbach plexus
- 2types of neurons
  - Ascending neuron
  - Descending neuron
- When bolus produces the stretch serotonin is released
- Activation of ascending neuron coil release 2 neuron

Substance P   Acetylcholine

↓

Works on muscarininc receptors (Gq)

↓

↑Ca

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- Whenever there is activation of Gq muscarmic receptor there is contraction of smooth muscle proximal to the bolus
- Descending neuron will release

↓

Nitric oxide & VIP

↓

Vasodilators

↓

Release the muscle

↓

Movement of food forward

↓

Peristalsis

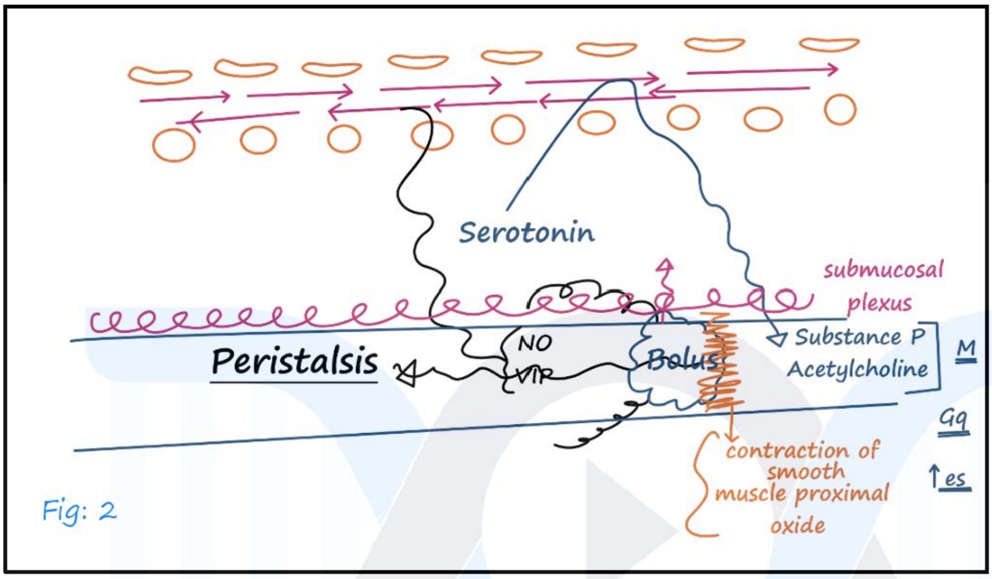

Serotonin
submucosal plexus
Peristalsis
NO
VIP
Bolus
Substance P
Acetylcholine
M
Gq
↑es
contraction of smooth muscle proximal
oxide

Fig: 2

- In segmental movement contraction occurs at both ends

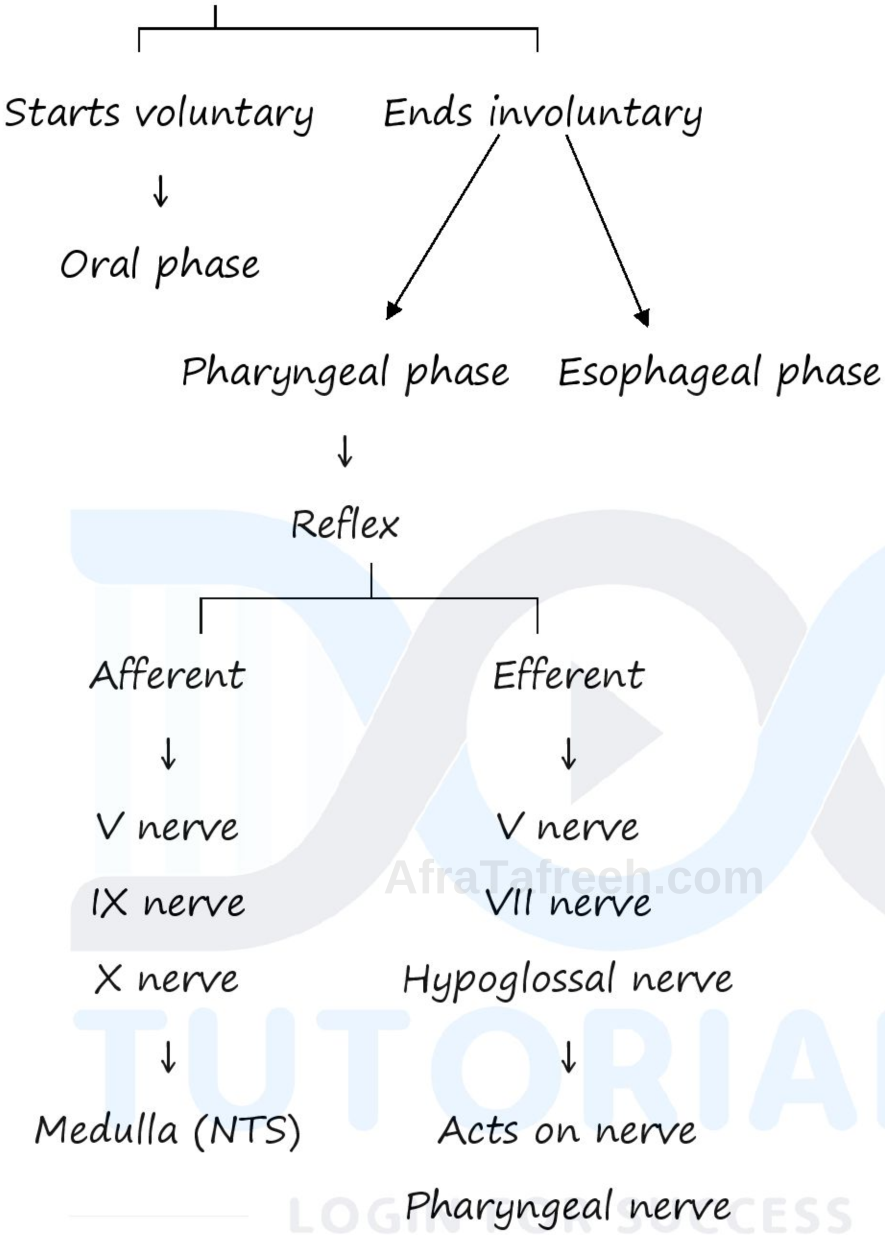
↓

Bolus is broken intro multiple fragments

Mixing/absorption of food

Deglutition

- Swallowing of food


Starts voluntary
Oral phase
Ends involuntary
Pharyngeal phase
Esophageal phase
Reflex
Afferent
V nerve
IX nerve
X nerve
Medulla (NTS)
Efferent
V nerve
VII nerve
Hypoglossal nerve
Acts on nerve
Pharyngeal nerve

Esophageal motility

- Peristalsis 3 types
- 1° peristalsis
  - Most physiological
  - As we start swallowing food primary physiology peristalsis stams
  - Progressive

- 2° peristalsis
  - Progressive
  - Due to irritation of esophagus
- 3° peristalsis
  - Always pathological
  - Non progressive → Mainly leads to spasm of esophagus

Achalaria cardia

- Absence of NO → Relaxation problem
- Unopposed contraction at level of LES
- Treatment: Botox injection

After esophageal motility

- Stomach is plastic → Receptive relaxation in proximal portion → Relaxation of muscle
- Can accommodate food
- P = 2T/R, If ↑ radius, tension ↑

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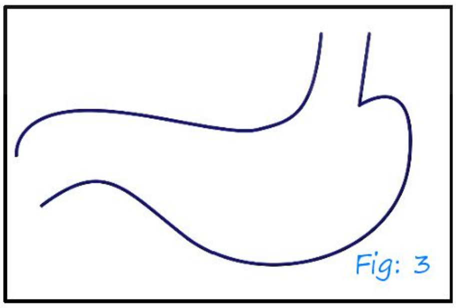


Fig: 3

- After food is received retropulsion → Mixing to grinding of food

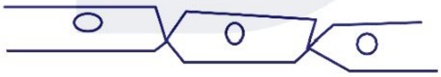
Factors ↑ gastric emptying	↓ Gastric emptying
• Gastrin • Distension of stomach by food	• CCK • Entero gastric reflux • Undigesting food particle in colon • Decreased gastric emptying

Small intestine

- 2 types of movement

Segmentation

↓

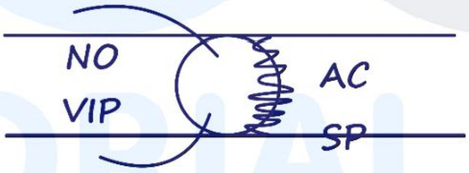


↓

Digestion and absorption of food

Peristalsis

↓



Large intestine

- Proximal colon & Distal colon
- Absorption of water
- Storage of fecus

Absorption of water, Storage of fecus — Function

- 2 types of movements

Haustrations
↓
Combined contraction
of circular and
longitudinal muscle
Exclusive in only
proximal colon
'absorption of
electrolytes and water

Mass movements
↓
Movemenst of one seg
into other segment
↓
Rectal distension
↓
Defecation reflex

Defection reflex 00:33:07

- 2 sphincters

Internal
↓
Involuntary
Smooth muscle

External
↓
Voluntary
Skeletal muscle
Pudendal nerve

Sympathetic
↓
Inhibits
defecation

Parasympathetic
↓
Facilitate defection
Relaxation of internal
anal sphincter

- Motility in empty stomach is called migratory motor complex
- When empty → No cell will release motilin hormone ← Erythromycin/Azithromycin
- MMC occurs every 90 mins
- Purpose – To clean GIT before next meal
- Hence called House Keeping waves

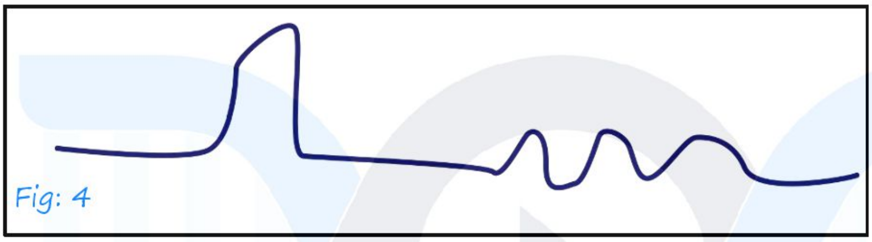
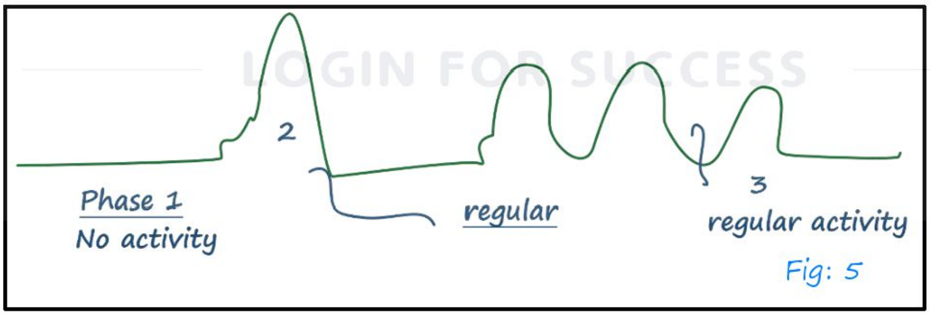


Fig: 4

Phase

- 1-No activity
- 2-Irregular activity
- 3-Regular activity


2
Phase 1
No activity
regular
3
regular activity
Fig: 5

GIT HORMONES

- Basically, divided into 2 categories
  - **Gastrin**
    - Gastrin ↑ G cell
    - CCk-PZ ↑ I cell
  - **Secretin**
    1. Secretin ← S cell
    2. VIP
    3. GIP ← K cell
    4. GLP ← L cell

    (3, 4) — Incretin

- Mo cells releases motilin → Motilin migratory complex
- Ghrelin

Gastrin

- G cells releases gastrin hormone
- Increase HCL secretion
- G cells are present on antrum of stomach
- Receptor → CCK-B
- Factors that increase and decrease gastrin service

Decrease	**Increase**

• Acid increase • Somatostatin • GIP • Secretin	• Distension – Antral part • Ca^{2+} • Amino acids • Peptides • Epinephrine

- Most important function is increase HCL produced by oxyntic/ parietal cell
- They also stimulate chief cell to release pepsin
- They also help in growth of GIT mucosa (Trophic)

CCK-PZ 00:06:02

- CCK cause increase gall bladder contraction (cologogue) by relaxation of sphincter of oddi → Bile secretion
- PZ –
  - PancreoZymin
  - Stimulate pancreatic secretion
  - Decreases gastric emptying
  - Also augments action of secretin
  - Same role as gastrin
  - Trophic to gastric mucosa
  - Increase satiety → decrease hunger

DOT TUTORIALS
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Secretin 00:09:10

- Natural antacid
- First hormone that was discovered (Bayliss and starling)

↓

Given the term hormone

- Produced by S cell
- Natural antacid ← increase HCO_3
- Inhibit gastrin → decrease gastric acid
- Contraction of pyloric sphincter

VIP 00:11:28

- Causes relaxation
- Increases fluids and electrolytes
- When there is vasodilatation → can cause more entry of things

Incretin

2 hormones

K — L

GIP ↓ Glucose dependent insulinotropic peptide

GLP ↓ Glucagon like peptide

working on β cells

- ATP sensitive K^+ channels → increase K^+ Ca^{2+} → insulin

- Receptor for GIP and GIP directly releases insulin
- GLP–1 Agonists
  - Treatment of DM
  - Side effects injections
  - Drugs
- Exenatide
- Liraglutide
- Decrease sugar and body weight

Decrease weight and treatment Dm

- GLP + 1 agonists
- SGLT2 blockers
- GLP – 1
- GIP]– Degraded by DPP – 4

↓

DDP 4 inhibitor

↓

Sitagliptin

Vildagliptin

Sexagliptin

Linagliptin

Alegliptin

Linagliptin safe in renal disease

Motilin 00:16:42

- Released from Mo cells

- Cause migratory motor complex
- Housekeeping waves → cleaning of GIT before next meal
- Erythromycin works on MMC and cause diarrhea

Ghrelin 00:17:39

- Increases food intake
- Whenever stomach empty → ghrelin is released → increase hunger
- Increases growth hormone / gastric motility / gastric acid secretion
  - Whenever there is fat → leptin in released → decrease hunger
  - B cells → somatostatin released

    ↓

    Universal inhibitory hormone because it decreases
    - Gut motility
    - GIT secretion
    - Insulin
    - Glucagon
    - Growth hormone

GIT SECRETION

Salivary Secretion 00:00:20

- Maximum potassium content – colon
- Maximum potassium secretion – Saliva
- PH of saliva: 6-6.5 (Hypotonic)

  ↓ * 1.5 L/day

  H^+/HCO_3^+
- 2 types of salivary gland

Major

↓

i. Parotid gland (largest) (20%)

ii. Submandibular (max → 70%, secretion)

iii. Sublingual (10%)

Minor

↓

Von – Ebner

↓

Salivary lipase is secreted

Ptylin

↓

Carbohydrate digestion

Lingual lipase

↓

Fats digestion

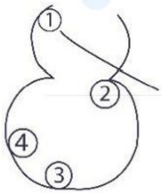
– No enzymes for protein digestion

- IgA/Lysozymes are present
- Salivary gland is under the control of autonomic nervous system

ANS

- Sympathetic control
  ↓
  Saliva become thick
- Parasympathetic control
  ↓
  More of watery saliva
  - CN IX
    ↓
    Otic ganglion
    ↓
    Parotid gland
  - CN VII
    ↓
    Submandibular ganglion
    - Submandibular gland
    - Sublingual gland

Gastric Secretion 00:06:01

- Maximum secretion per day – 2.5 litre
- 

Flask shaped gastric gland
  1. Surface cell
  2. Neck cell
  3. Parietal cell
  4. Chief cells

– Surface cell –

- a. rich in acid, they produce bicarbonate rich mucous.

↓

- b. Important for immunity

- Neck cell → stem cells can be formed
- Parietal cell → also called oxyntic cell

HCL Intrinsic factor of castle

↓

(Extrinsic factor → B_{12})

Autoimmune antibody

↓

Antibody against oxyntic cell

↓

Fernicious anemia

HCl

- Chief cells produce pepsinogen ⟶ pepsin

  G cell are present in antral region to produce gastrin
- Enterochromaffin cells → produces histamine and increases the production of HCL
- Whenever antihistaminics → H_2 blockers like rantidine, cimetidine are given.

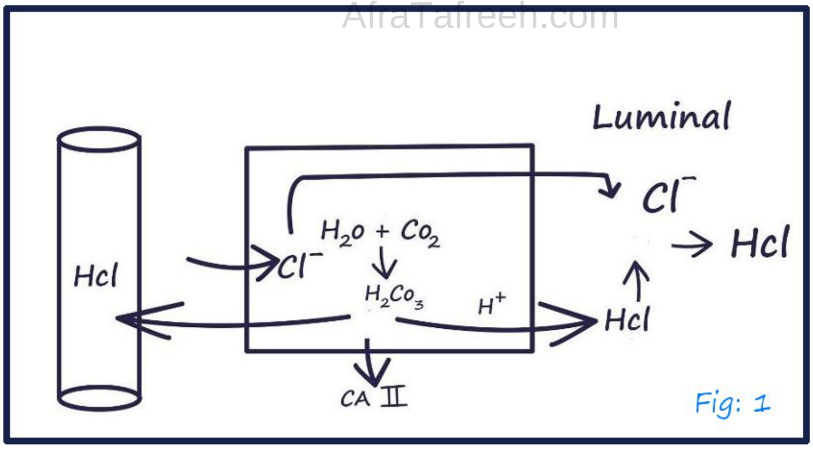


Fig: 1

- $H_2O + CO_2 \rightarrow H_2CO_3$

↓

Under the influence of carbonic anhydrase 2

HCO_3 ↓ Enters blood vessel and Cl^- enter cell ↓

H^+ ↓ Needs proton pump (1^o active pump) ↓

Enters lumen combines with H^+

↓

HCl

Receptors that affect production of HCl

- H_2 Receptor → Histamine will activate
- CCK receptor → activated by gastrin
- Muscarinic receptor → parasympathetic activation

↓

Acetylcholine

- Activate proton pump

↓

H^+ efflux

↓

More HCl production

Decrease proton pump

- Increases HCl inhibits proton pump
- Somatostatin decreases gastric secretion/motility
- Prostaglandins also inhibit HCl.
- Enzymes to digest protein

Pepsinogen
↓ HCl
Pepsin
↓
Helps in digestion of proteins

No hormone for digestion of carbohydrates

Gastric lipase
↓
Digest fat

Phases of Gastric secretion

1. Cephalic phase → thinking of food → salivation (20%)
2. Gastric phase → 70% → most important
3. Intestinal phase → 10%

Pancreatic juice

- Enzymes are in precursor form to prevent autodigestion
- pH of pancreatic juice – 8/HCO_3^-/Highest protein content

Peptidase

Exopeptidase ↓
- Carboxypeptidase
- Aminopeptidase

Endopeptidase ↓
- Trypsin
- Chymotrypsin

Lipase/Co-lipase/Amylase/Nuclease/Disaccharidase

$$\text{Trypsinogen} \xrightarrow{\text{Enterokinase}} \text{Trypsin}$$

Trypsin ↓ remove AA

$$\text{Chymotrypsinogen} \xrightarrow{\text{Trypsin}} \text{Chymotrypsin}$$

Regulation

Secretin ↓
Increases HCO_3 content

CCK – P2 ↓
Increases GB contraction
Increases pancreatic enzyme

DOC TUTORIALS
LOGIN FOR SUCCESS

Bile

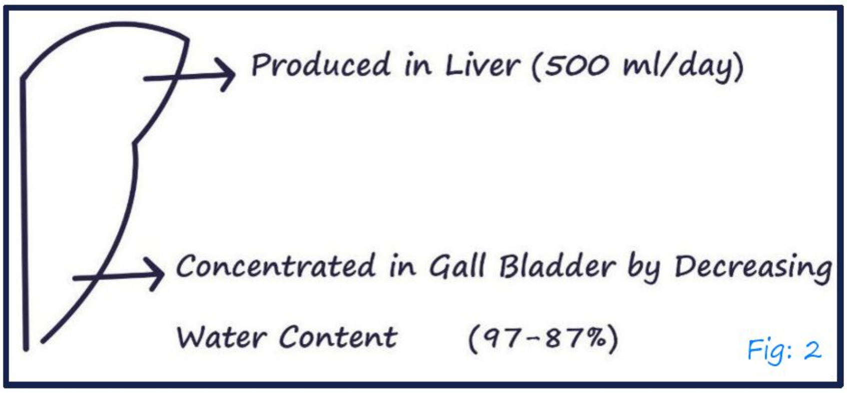

Produced in Liver (500 ml/day)
Concentrated in Gall Bladder by Decreasing Water Content (97-87%)

Fig: 2

Composition of bile

1. Bile acids → 1° bile acids → cholic acid
1° bile acids → Chendeoxycholic acid
On bac. Action ↓
Bile acids → 2° bile acid
2° bile acid → Deoxycholic acid, Lithocholic acid

2.Bile salt

3.Bile pigment

4.Cholesterol

- Bile acids are conjugated in liver + → Glycine
  ↘ Taurine

Bile Salts

- Na and K^+ salts
- Sodium glycocholic acid
- Digest the fat and absorption of fat → for excretion of cholesterol and bile pigment

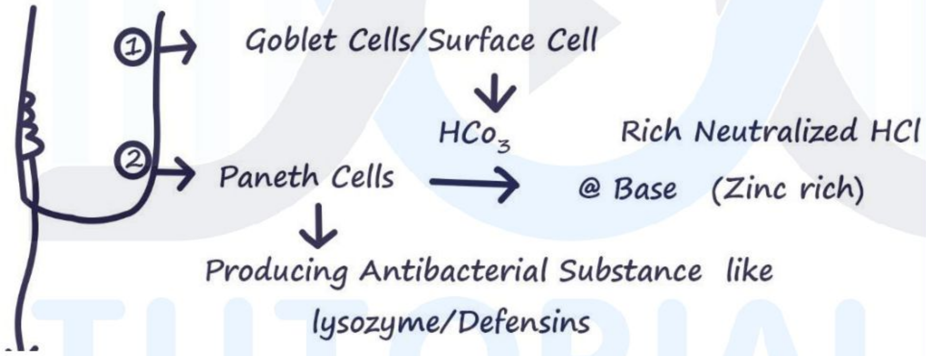
I. Chologogue – Substances that increases GallBladder contraction, CCK – PZ relaxes sphincter of oddi

II. Choleretics

- Increase bile formation
- Most potent → bile salt themselves
- Secretin and vagal stimulation

Intestinal Secretion 00:31:23

- Released from crypts of Leiberkuhn


①
Goblet Cells/Surface Cell
HCO_3
Rich Neutralized HCl
②
Paneth Cells
@ Base (Zinc rich)
Producing Antibacterial Substance like lysozyme/Defensins

Epithelial cells → secretion called succus entericus

Fig: 3

1. Lingual lipase is secreted by

a. Parotid gland
b. Submandibular gland
c. Sublingual gland
d. Ebner's gland

2.Highest daily secretion of potassium is in

a. Saliva
b. Bile
c. Pancreatic secretion
d. Jejunal secretion

3.The intrinsic factor of castle is secreted by which of the following in gastric glands

a. Goblet cells
b. Chief cells
c. Parietal cells
d. Enterochromaffin cells

4.Gastric secretion is increased by all except

a. HCl
b. Histamine
c. Acetyl choline
d. Gastrin

5.Which of the following is the most potent choleretic?

a. CCK

b. Fatty acid

c. Bile salts

d. Amino acids

6.Enterohepatic circulation is necessary for the secretion of

a. Intestinal juice

b. Pancreatic juice

c. Bilirubin

d. Bile salt

DIGESTION & ABSORPTION

Digestion of Carbohydrate 00:00:02

- Digestion of carbohydrate starts in saliva itself

  ↓

  Activated by Cl^-

  Deactivated by acidic

- 90-95% of digestion → pancreatic amylase

  ↓

  Converts complex carbohydrate (starch) into simpler form

  ↓

  Disaccharides/Trisaccharides

  ↓

  Monosaccharaides

  (Glucose, fructose galactose)

- Absorption is by
  - 2° Active transport
  - Facilitated diffusion (passive)

2° active transport

↓

SGLT

1 2

Both are present in kidney for reabsorption of glucose

- But in the kidney, – 90% absorption is by SGLT-2
  - 10% absorption is by SGLT-1
- Hence in DM – SGLT 2 inhibitors are given

  ↓

  Canagliflozin
- In intestine → only SGLT 1 is present on the luminal side

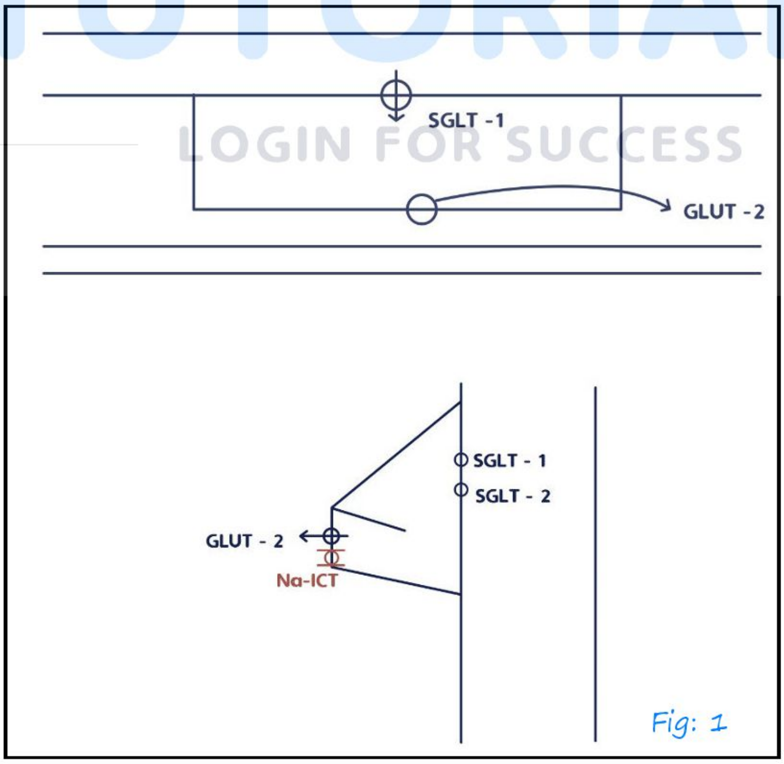

SGLT -1
GLUT -2
SGLT - 1
SGLT - 2
GLUT - 2
Na-ICT

Fig: 1

Facilitated diffusion

- Does not require ATP
- GLUT- 1 – BBB /RBC/placenta
- GLUT-2 – β cells, liver, intestine, kidney
- GLUT-4 → insulin dependent GLUT
  - → present in skeletal muscle, adipose tissue
- GLUT-5 – fructose

FAT 00:07:33

- Digestion of fats starts in saliva → Lingual lipase
  - → Stomach – Gastric lipase
  - → Pancreas – Pancreatic lipase
  - Colipase
  - Cholesterol ester
- Breakdown Triglycerides into → Monoglycerides
  - → Cholesterol
  - → Fat soluble vitamins

↓

Incorporated in transport vesicle called as micelles

↓

High concentrated free fatty acid

↓

Easily absorbed by passive diffusion

↓

FFA will be converted into TG and transported by chylomicrons

DOC TUTORIALS LOGIN FOR SUCCESS

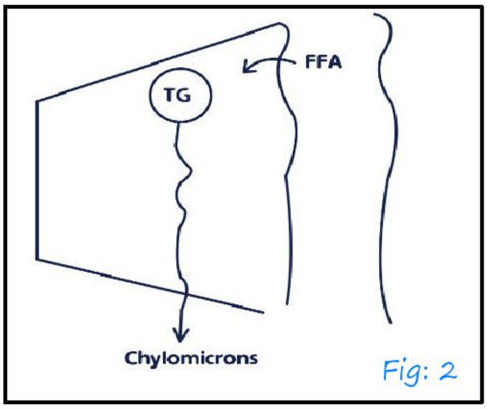

FFA
TG
Chylomicrons

Fig: 2

- Bile is absorbed in the terminal ileum and again go back to liver

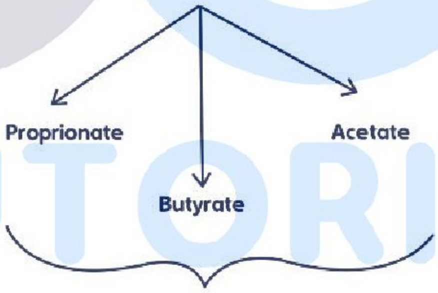
↓

Enterohepatic circulation of bile (5-8 times/day)

↓

Demand of the bile reduced

- Short chain FA- formed at level of colon (bacteria)


Proprionate
Butyrate
Acetate

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- Trophic action @ level of intestine
- Absorbed in exchange of H+

↓

pH regulation

- Have anti-inflammatory property as well

Protein 00:14:57

- Protein cannot be digested in saliva
- Stomach → pepsin/renin +
- pancreas → trypsin
  → chymotrypsin

Endopeptidase
↓
Act on interior region

- Exopeptidase → act on end region

Carboxy peptidase   Amino peptidase

Protein

Dipeptide   Tripeptide

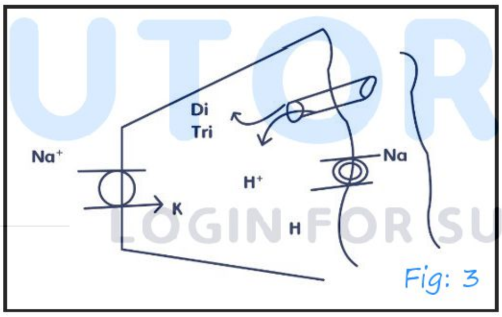

Fig: 3

- Protein is absorbed in the form of dipeptide & tripeptide
- Along with them proteins are released
- Protons are taken up by sodium proton exchanger
- Sodium goes into basolateral membrane and exchanges with Na^+ K^+ pump

- Amino acids are produced and they are in the circulation

Vitamins 00:18:18

- Vitamin's
  - Fat soluble → micelles
  - Water soluble → absorbed by sodium dependent co Transporter

↓

Except folate and vitamin B12 → sodium independent

Iron 00:19:36

- Absorbed in duodenum

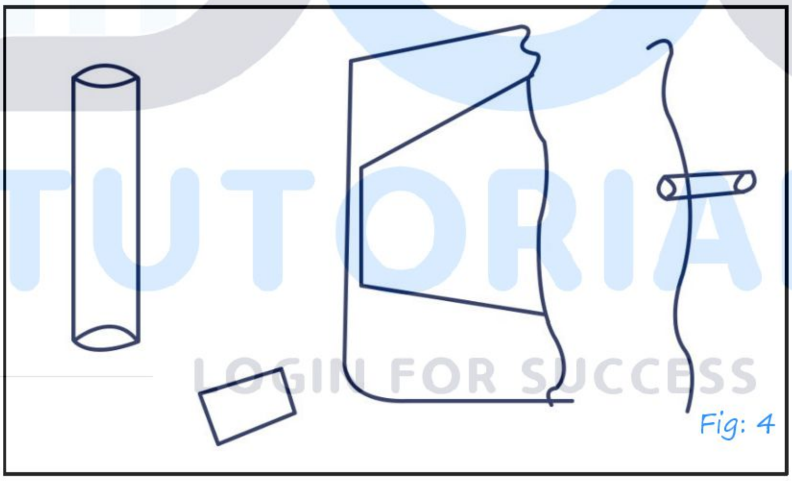

Fig: 4

- In diet, Fe^{3+} from +
- Ferric $\xrightarrow[\text{reductase}]{\text{Ferric}}$ Ferrous

↓ DMT-1 divalent metal transport Absorbed

TUTORIALS LOGIN FOR SUCCESS

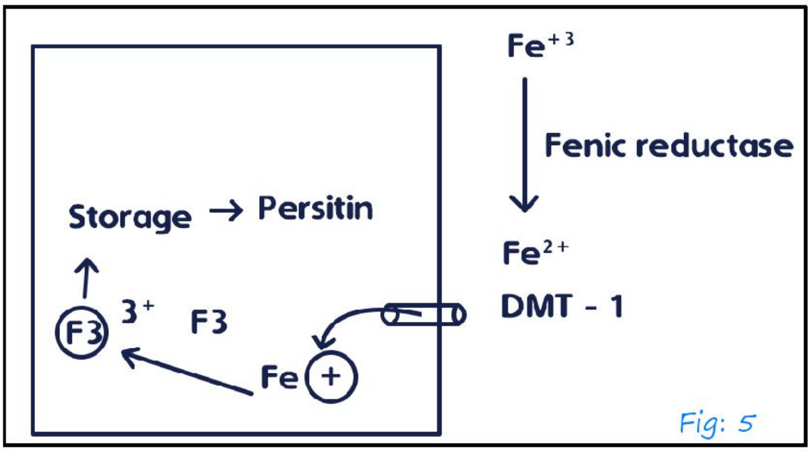

Fig: 5

- Iron is stored in the ferrous form
- Extra iron is stored in the form of ferritin
- Enters blood in the form of Fe2+ by ferroprotein

↓

Helps absorption of ferrous ion

↓ Hephastin

Ferric

↓

Moves into blood circulation Transferrin

- In liver, hepcidin inhibits ferroprotein to prevent ion overloading
- Mutation of hepcidin protein → iron overloading

↓

Hemochromatosis

- Hepcidin – type of negative feed back
- All major nutrients are maximally absorbed in jejunum – H_2O, long chain fatty acids → lacteal

→ chylomicron

- In duodenum – Fe2+ /Ca^{2+}
- In ileum – vitamin B12 /Mg2+ / Bile salt
- Gut → colon microflora → Vitamin B12